# Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy (Review)

**Di Nisio M, Porreca E, Ferrante N, Otten HM, Cuccurullo F, Rutjes AWS**


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[Intervention Review]

# Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

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## ABSTRACT

### Background

Venous thromboembolism (VTE) often complicates the clinical course of cancer disease. The risk is further increased by chemotherapy but the safety and efficacy of primary thromboprophylaxis in cancer patients treated with chemotherapy is uncertain.

### Objectives

To assess the efficacy and safety of primary thromboprophylaxis in ambulatory cancer patients receiving chemotherapy.

### Search methods

The Cochrane Peripheral Vascular Diseases Group searched their Specialised Register (last searched 3 May 2011) and CENTRAL (2011, Issue 2). The authors searched clinical trials registries and reference lists of relevant studies.

### Selection criteria

Randomised controlled trials (RCTs) comparing unfractionated heparin (UFH), low molecular weight heparin (LMWH), vitamin K antagonists (VKA), direct thrombin inhibitors, direct factor Xa inhibitors or mechanical intervention to no intervention or placebo; or comparing two different anticoagulants.

### Data collection and analysis

Data were extracted on methodological quality, patients, interventions and outcomes including symptomatic VTE and major bleeding as the primary effectiveness and safety outcomes, respectively.

### Main results

Nine RCTs with a total of 3538 patients were considered. None of the RCTs tested UFH, fondaparinux, direct factor Xa inhibitors or mechanical interventions. Overall, the risk of bias was low in most of the studies. LMWH, when compared with inactive control, significantly reduced the incidence of symptomatic VTE (risk ratio (RR) 0.62, 95% confidence interval (CI) 0.41 to 0.93) with no evidence of heterogeneity ($I^2$ = 0%). The number needed to treat to prevent a symptomatic VTE was 60. LMWH was associated with a

60% increase in major bleeding when compared with inactive control, although this was not statistically significant (RR 1.57, 95% CI 0.69 to 3.60; $I^2$ = 10%). There was a 45% reduction in overall VTE (RR 0.55, 95% CI 0.34 to 0.88; $I^2$ = 0%) while for symptomatic pulmonary embolism, asymptomatic VTE, minor bleeding and one-year mortality the differences between the LMWH and control groups were not statistically significant. The effect of the vitamin K antagonist warfarin on preventing symptomatic VTE, measured in only one study, was not statistically significant (RR 0.15, 95% CI 0.02 to 1.20). In one RCT of patients with myeloma, LMWH was associated with a 67% reduction in symptomatic VTE (RR 0.33, 95% CI 0.14 to 0.83) compared with warfarin, with no differences in major bleeding. Antithrombin, evaluated in one study on paediatric patients, had no significant effect on VTE nor major bleeding when compared with inactive control.

**Authors' conclusions**

Primary thromboprophylaxis with LMWH significantly reduced the incidence of symptomatic VTE in ambulatory cancer patients treated with chemotherapy. However, the lack of power hampers definite conclusions on the effects on major safety outcomes, which mandates additional studies to determine the risk to benefit ratio of LMWH in this setting.

## PLAIN LANGUAGE SUMMARY

**Protective treatment against blood clots in non-hospitalised cancer patients receiving chemotherapy**

Cancer patients are more likely than patients without cancer to develop blood clots in their veins (venous thromboembolism), either in the lungs (pulmonary embolism) or the deep venous system (deep vein thrombosis or DVT). Chemotherapy further increases this risk. Yet bleeding at the site of the cancer and a relative decrease in number of platelets in the blood (thrombocytopenia) caused by the chemotherapy may make cancer patients more likely to have bleeding complications with blood thinning agents. This systematic review looked at the effectiveness and safety of blood thinning agents (anticoagulants) when used to prevent blood clots in cancer patients receiving chemotherapy. Nine randomised controlled studies with a total of 3538 patients investigated the prevention of blood clots in patients without a history of blood clots. The use of low molecular weight heparin was associated with a reduction in blood clots (the number needed-to-treat to prevent a symptomatic blood clot was 60) without any clear benefit in survival as the number of major bleeding events was increased, although this was not statistically significant and further study is needed. The findings from two studies of the vitamin K antagonist warfarin, one comparing warfarin with low molecular weight heparin in patients with myeloma, were too limited to support a beneficial effect of warfarin in the prevention of blood clots in cancer patients. Antithrombin was evaluated in one study in children and had no significant effect on blood clots or major bleeding when compared with an inactive control.

Overall the studies had a low risk of bias but the small number of studies, participants and clinical events prevented the review authors from making definite conclusions on the effectiveness of these medications. For the same reasons, we could not determine if the treatment effect differed with age (below 65 years or above 65 years), type of cancer or stage of cancer (metastatic versus non metastatic). None of the studies tested other anticoagulant treatment including unfractionated heparin, fondaparinux, direct factor Xa inhibitors or mechanical interventions (intermittent pneumatic compression and graduated elastic stockings).

## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

**Low molecular weight heparin (LMWH) compared with placebo or no LMWH for primary thromboprophylaxis in ambulatory cancer patients receiving chemotherapy**

**Patient or population:** ambulatory cancer patients receiving chemotherapy
**Settings:** outpatient clinics
**Intervention:** LMWH
**Comparison:** placebo or no LMWH

| Outcomes | Illustrative comparative risk (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Placebo or no anticoagulant | LMWH | | | | |
| Symptomatic VTE | 44 per 1000 | 27 per 1000 | RR 0.62 [0.41, 0.93] | 2464 (6) | ⊕⊕⊕ moderate[1] | |
| Major bleeding | 11 per 1000 | 18 per 1000 | RR 1.57 [0.69, 3.60] | 2394 (5) | ⊕⊕ low[3] | |
| Symptomatic PE | 8 per 1000 | 5 per 1000 | RR 0.63 [0.21, 1.91] | 1710 (3) | ⊕⊕ low[2] | |
| 1-year mortality | 503 per 1000 | 523 per 1000 | RR 1.04 [0.92, 1.16] | 1848 (4) | ⊕⊕⊕⊕ high | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio.
GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Downgraded (1 level) because for 3 out of 6 studies it was unclear if adequate concealment of allocation was used
[2] Downgraded (2 levels) because out of 6 included studies, only 3 report symptomatic PE; the 95% CI includes both negligible effect and appreciable benefit or appreciable harm.
[3] Downgraded (2 levels) because for 2 out of 5 contributing studies it was unclear if adequate concealment of allocation was used; the 95% CI includes both negligible effect and appreciable benefit or appreciable harm

## BACKGROUND

Cancer is often complicated by venous thromboembolism (VTE), which can present as deep vein thrombosis (DVT) or pulmonary embolism (PE), or both (Khorana 2009). Cancer patients with VTE have a two-fold or greater increased mortality compared to cancer patients without thrombosis, which could be explained by the development of fatal PEs or by a worse prognosis for patients with those cancers complicated by VTE (Sorensen 2000). VTE in cancer patients may be hard to recognise due to aspecific symptoms which may overlap and be confused with those caused by the underlying cancer disease process or cancer treatments. VTE carries significant morbidity due to the need for hospitalisation and an increased risk of recurrent VTE or bleeding complications, or both, while on anticoagulation (Hutten 2000; Prandoni 2002). The occurrence of (unrecognised) VTE may delay the delivery of cancer treatments such as chemotherapy with a further negative impact on morbidity and, potentially, mortality. In addition, the occurrence of venous thromboembolic events brings further emotional strain for patients and their families, which negatively impacts their quality of life. Finally, the costs related to the management of VTE may be considerable, resulting from the expenses related to drugs and hospitalisation.

### Description of the condition

The incidence of VTE is higher in patients with cancer compared to those without cancer. As compared to an incidence of about 0.1% in the general population, the rate of VTE in patients with cancer has been reported to vary between 0.6% and about 8% (Khorana 2009). Chemotherapy has been recognised as an independent predictor for symptomatic VTE with reported rates of 11% (Otten 2004) up to 75% (Khorana 2009) depending on the type of chemotherapeutic agent used. The risk of thrombosis in cancer patients receiving chemotherapy seems to vary based on the stage of the disease, ranging from 3% to 5% in patients with early-stage cancer to 30% in those with metastatic or advanced malignancy (Khorana 2009). Current guidelines recommend secondary thromboprophylaxis during chemotherapy in cancer patients with a positive history of VTE (Lyman 2007), whereas the benefit-risk ratio of primary prophylaxis in such patients is not well established.

### Description of the intervention

Currently available drugs for the prevention of VTE are vitamin K antagonists, unfractionated heparin, low molecular weight heparins (LMWH) and fondaparinux. In fact, each one of these agents presents disadvantages for long-term prophylaxis in the ambulatory patient with cancer. Heparins and fondaparinux require daily subcutaneous injections, which represent a considerable burden for the patient. Vitamin K antagonists require frequent monitoring for dose adjustments and can be difficult to administer because of nausea and vomiting, poor nutrition and interaction with other medications. New oral anticoagulants such as direct thrombin and factor Xa inhibitors offer the potential advantages of oral route administration, absence of laboratory monitoring requirements, and fewer pharmacological interactions. In general, the use of anticoagulants in cancer patients is more challenging and is aggravated by a higher rate of recurrent thrombotic events and bleeding complications relative to patients without cancer (Hutten 2000; Prandoni 2002). In the study of Prandoni and colleagues the 12-month cumulative incidence of recurrent VTE and major bleeding were 20.7% and 12.4%, respectively, in patients with cancer compared to 6.8% and 4.9% in patients without cancer (Prandoni 2002). Interestingly, recurrent VTE and bleeding events were related to cancer severity and apparently were not explained by sub- or over-anticoagulation. Possible mechanisms underlying these associations include the procoagulant state induced by cancer and treatments for cancer (for example chemotherapy) as well as the decline in the patient's general condition leading to immobilization. Bleeding at the site of the cancer and the relative decrease in the number of platelets in the blood (thrombocytopenia) secondary to chemotherapy may at least partly explain the increase in bleeding events.

Currently available mechanical interventions for the prevention of VTE include intermittent pneumatic compression (IPC) and graduated elastic stockings (GES). These non-pharmacological interventions may be a valid option in cancer patients who are at risk of bleeding.

### Why it is important to do this review

The overall burden of VTE in patients with cancer is steadily increasing as a result of an aging population, greater awareness, frequent staging assessments using sensitive imaging techniques, prothrombotic anticancer treatments as well as the growing cancer population that is due to the aforementioned aging. Provision of widespread primary thromboprophylaxis for ambulatory cancer patients who receive chemotherapy may help prevent this treatable complication. However, the efficacy of thromboprophylaxis needs to be balanced against the risks, such as (major) bleeding events. We are not aware of any systematic review summarising the evidence on the benefits and risks of primary pharmacological prophylaxis in this setting.

## OBJECTIVES

Our main objective was to compare the efficacy and safety of primary thromboprophylaxis with placebo or no thromboprophylaxis in ambulatory patients with cancer receiving chemotherapy. The secondary objective was to compare the efficacy and safety of different types of primary thromboprophylaxis by stratifying the main results per type of drug and mechanical intervention, and by aggregating results from head-to-head comparisons.

# METHODS

## Criteria for considering studies for this review

### Types of studies

All randomised and quasi-randomised trials were eligible.

### Types of participants

Ambulatory outpatients of any age (including paediatric patients) with either a solid or haematological cancer, at any stage, and receiving chemotherapy were eligible. Studies that included patients with a positive history of VTE at enrolment were excluded if data could not be extracted separately for those without previous VTE. Studies evaluating prophylaxis for catheter-related thrombosis were excluded since this is already the subject of another Cochrane review (Akl 2011).

### Types of interventions

Interventions included any oral or parenteral anticoagulant (for example unfractionated heparin, low molecular weight heparin, vitamin K antagonists, direct thrombin or factor Xa inhibitors) or mechanical intervention (intermittent pneumatic compression or graduated elastic stockings), or both, used to prevent VTE in ambulatory patients with cancer that were receiving chemotherapy. Comparison interventions included either an inactive control intervention (placebo, no treatment, standard care) or an active control intervention (a different scheme or regimen of the same intervention, a different pharmacological type of prophylaxis, a different type of non-pharmacological prophylaxis). Any frequency or duration of administration, dosage or intensity and timing of delivery of pharmacological prophylaxis were considered.

### Types of outcome measures

#### Primary outcomes

The main effectiveness outcome was symptomatic VTE objectively verified by means of Doppler (compression) ultrasonography or venography for DVT and spiral computed tomography, ventilation/perfusion lung scan, or pulmonary angiography for PE. The main safety outcome was major bleeding, typically defined as including: overt bleeding associated with a fall in haemoglobin of 2 g/dL or more or leading to a transfusion of two or more units of packed red blood cells or whole blood; bleeding that occurred at a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal); or bleeding contributing to death.

#### Secondary outcomes

Secondary outcomes included symptomatic PE; symptomatic DVT; asymptomatic VTE; overall VTE; minor bleeding; one-year overall mortality; arterial thromboembolic events; superficial thrombophlebitis; quality of life; number of patients experiencing any adverse event, and patients experiencing any serious adverse event. Minor bleeding was defined as a bleeding event not matching the criteria for major bleeding. Serious adverse events were defined as events resulting in inpatient hospitalisation, prolongation of hospitalisation, persistent or significant disability, congenital abnormality or birth defect of offspring, life-threatening events or death. For trials using low molecular weight heparin as the intervention or control, heparin-induced thrombocytopenia (HIT) and the incidence of osteoporosis, as defined by the authors, were recorded. We considered all outcomes as binary outcomes except for quality of life, which was considered as a continuous outcome.

## Search methods for identification of studies

### Electronic searches

The Cochrane Peripheral Vascular Diseases Group searched their Specialised Register (last searched 3 May 2011) and the Cochrane Central Register of Controlled Trials (CENTRAL) (2011, Issue 2), which is part of *The Cochrane Library* at www.thecochranelibrary.com. See Appendix 1 for details of the search strategy used to search CENTRAL. The Specialised Register is maintained by the Trials Search Co-ordinator and is constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL and AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used, are described in the Specialised Register section of the Cochrane Peripheral Vascular Diseases Group module in *The Cochrane Library (* www.thecochranelibrary.com).

The authors searched the following clinical trial registries (up to April 2011) to identify ongoing trials:

- www.clinicaltrials.gov;
- www.controlled-trials.com;
- www.actr.org.au.

### Searching other resources

We searched reference lists of identified studies and contacted content experts and trialists for relevant references. Conference proceedings of the American Society of Clinical Oncology and the International Society of Thrombosis and Haemostasis were screened up to April 2011 by one review author and any study included if adequate information could be obtained either from the abstract or from personal communication.

## Data collection and analysis

### Selection of studies

Two review authors independently reviewed titles and abstracts from the database searches to determine whether the inclusion criteria were satisfied. Any disagreement was resolved through discussion between the review authors. The review authors were not blinded to the journal, institution or results of the study. No language restrictions were applied. Studies with insufficient information were reassessed if additional information became available from the authors. Reasons for excluding studies were documented. In the event of multiple reports relating to the same trial, we considered them all.

### Data extraction and management

Two review authors independently extracted the data from the included studies on standardised forms and any disagreements were resolved by consensus. Collected information included methodological quality, characteristics of patients participating in the studies, characteristics of the intervention and control groups, and outcome characteristics of every group of participants. Whenever possible, we extracted results from an intention-to-treat analysis. If effect sizes could not be calculated, we contacted the authors for additional data.

### Assessment of risk of bias in included studies

Two review authors independently assessed randomisation, blinding and adequacy of analyses (Juni 2001; Rutjes 2009). Disagreements were resolved by consensus.

Two components of randomisation were assessed: generation of allocation sequence and concealment of allocation. Generation of allocation sequence was considered adequate if it resulted in an unpredictable allocation schedule. Mechanisms considered to be adequate included random-number tables, computer-generated random numbers, minimisation, coin tossing, shuffling cards and drawing lots. Trials using an unpredictable allocation sequence were considered randomised. Trials using potentially predictable allocation mechanisms, such as alternation or allocation of patients according to date of birth, date of presentation or case record number, were considered quasi-randomised.

Concealment of allocation was considered adequate if patients and investigators responsible for patient selection were unable to predict before allocation which treatment was next. Methods considered adequate included central randomisation; pharmacy-controlled randomisation using identical prenumbered containers; and sequentially numbered, sealed, opaque envelopes. Blinding of patients and therapists was considered adequate if experimental and control preparations were explicitly described as indistinguishable or if a double-dummy technique was used. Assessors were considered blinded if this was explicitly mentioned by the investigators.

Analyses were considered adequate if all randomised patients were included in the analyses according to the intention-to-treat principle. The item 'free of selective reporting' was classified as at low risk of bias if we had both the protocol and the full report of a given study, where the full report presented results for all outcomes listed in the protocol. We classified a study at high risk of bias if a report did not present data on all outcomes reported in either the protocol or the methods section. The risk of bias item 'free of other bias' was not considered in this review. We assessed the reporting of primary outcomes and sample size calculations. Finally, we used GRADE to describe the quality of the overall body of evidence (Guyatt 2008; Higgins 2008), which was defined as the extent of confidence in the estimates of treatment benefits and harms.

### Measures of treatment effect

Results are shown as summary risk ratios (RRs) for dichotomous variables; a 95% confidence interval (CI) was determined for each estimate. In the case of statistically significant overall estimates, we also calculated clinical effect summary statistics such as the number needed to treat to benefit one patient (NNT) or the number needed to treat to harm one patient (NNH) to express the final results of the review.

### Assessment of heterogeneity

Heterogeneity of the treatment effect between trials was measured using the $I^2$ statistic (Higgins 2003), which describes the percentage of total variation across trials that is attributable to heterogeneity rather than to chance. $I^2$ statistic values of 25%, 50% and 75% may be interpreted as low, moderate and high between-trial heterogeneity, respectively, although the interpretation of $I^2$ depends on the size and number of trials included (Rücker 2008).

### Assessment of reporting biases

We evaluated publication bias and other biases related to small study size using funnel plots, plotting effect sizes on the vertical axis against their standard errors on the horizontal axis. We assessed asymmetry by the asymmetry coefficient, the difference in effect size per unit increase in standard error (Sterne 2001), which is mainly a surrogate for sample size. Symmetry would be expected in the absence of any bias related to small study size. Any anomaly was further explored in stratified analyses in which we investigated the effects of differences in types of LMWH and suboptimal design choices on the magnitude of the effects.

### Data synthesis

In the main analyses, data were analysed and presented by stratifying for the type of thromboprophylaxis used.

We planned to explore the between trial heterogeneity by stratifying the main outcomes for the following trial characteristics: age (below 65 years versus above 65 years); type of cancer, stage of cancer (metastatic versus non-metastatic); type of major bleeding (according to definition versus unclear or different definition); concealment of allocation (adequate versus inadequate or unclear); blinding (adequate versus inadequate or unclear); analysis in accordance with the intention-to-treat principle (yes versus no or unclear); trial size; and differences in the use of co-interventions in the trial groups. We planned to use univariate random-effects meta-regression models (Thompson 1999) to determine whether treatment effects were affected by these factors and by three continuous variables at trial level: dosage of intervention, treatment duration and length of follow up. The data analysis was performed in RevMan version 5 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen).

# RESULTS

## Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.
See: Characteristics of included studies; Characteristics of excluded studies.

### Results of the search

There were 1328 citations retrieved from the CENTRAL search and 191 from the Peripheral Vascular Diseases Group Specialised Register. Following title and abstract screening, 35 were considered to be potentially eligible. Six additional ongoing studies were identified from the search of trials registries.
Following full text analysis there were 15 citations for nine studies that were included in the review and 16 citations to 16 studies which were excluded. There were 11 citations for ongoing studies.

### Included studies

The nine completed randomised controlled trials (RCTs) randomised a total of 3557 participants. None of the included RCTs used unfractionated heparin (UFH), fondaparinux, direct factor Xa inhibitors or non-pharmacological prophylaxis as the intervention.
Six studies assessed LMWH as the intervention:

- Agnelli 2009 recruited patients (n = 1150) with metastatic or locally advanced lung, gastrointestinal, pancreatic, breast, ovarian or head and neck cancer and randomised them to nadroparin (3800 IU anti-Xa subcutaneously (sc) once daily (od) versus placebo. Study treatment started on the same day as chemotherapy and was given for the duration of the chemotherapy or up to a maximum of 120 days (± 10 days);

- Altinbas 2004 recruited patients (n = 84) with histologically confirmed small cell lung carcinoma and randomised them to standard anticancer treatment with or without dalteparin (5000 IU sc, od). Dalteparin was stopped with disease progression or at the end of the 18 weeks of chemotherapy;

- Haas 2005 recruited patients (n = 532) with metastatic or locally advanced lung cancer who received chemotherapy. They were randomised to six months of certoparin (3000 IU sc, od) versus placebo. In a second study, the authors randomised 353 patients with advanced breast cancer to the same regimens. Despite the several emails that we sent to the lead author, we were unsuccessful in obtaining data on the second trial in advanced breast cancer patients. We therefore included the data presented in the abstract and in a related report (see Included studies);

- Kakkar 2004 recruited patients (n = 385) with histologically confirmed locally advanced or metastatic malignant disease of the breast, lung, gastrointestinal tract, pancreas, liver, genitourinary tract, ovary or uterus and randomised them to dalteparin (5000 IU sc, od) versus placebo. Study treatment was given for one year or until the patient died, whichever occurred sooner;

- Perry 2010 recruited patients (n = 186) with newly diagnosed, pathologically confirmed World Health Organization grade 3 or grade 4 glioma and randomised them to six months of dalteparin (5000 IU sc, od) versus placebo starting within the first month after surgery. Patients were allowed to continue the study medication for 12 months;

- Sideras 2006 recruited patients (n = 138) with advanced breast cancer who did not respond to first-line chemotherapy, advanced prostate cancer resistant to primary hormonal therapy, advanced lung cancer, or advanced colorectal cancer. In the first part of the study patients were randomised to dalteparin (5000 IU sc, od) versus placebo while in the second part patients were randomised to dalteparin (5000 IU sc, od) plus standard clinical care versus standard clinical care alone. Dalteparin (or placebo) was given for 18 weeks or until disease progression.

Levine 1994 recruited patients (n = 311) with metastatic stage IV breast carcinoma who had been receiving first-line or second-line chemotherapy for four weeks or less and randomised them to warfarin versus placebo. Study treatment began either at the start of chemotherapy or within the next four weeks and continued until one week after termination of chemotherapy.
Palumbo 2011 recruited patients (n = 667) with previously untreated myeloma who received thalidomide-containing regimens and randomised them to aspirin (100 mg/d), low-dose warfarin (1.25 mg/d), or low molecular weight heparin (enoxaparin 40 mg/d). The prophylaxis was administered during the three cycles of

induction therapy in patients ≤ 65 years and during the first six cycles of induction therapy in patients > 65 years.

Mitchell 2003 recruited paediatric patients (n = 85) newly diagnosed with acute lymphoblastic leukaemia. They were treated with L-asparaginase and a functioning central venous line was placed within two weeks of initiating induction chemotherapy. Patients were randomised to receive, or not, weekly infusions of antithrombin.

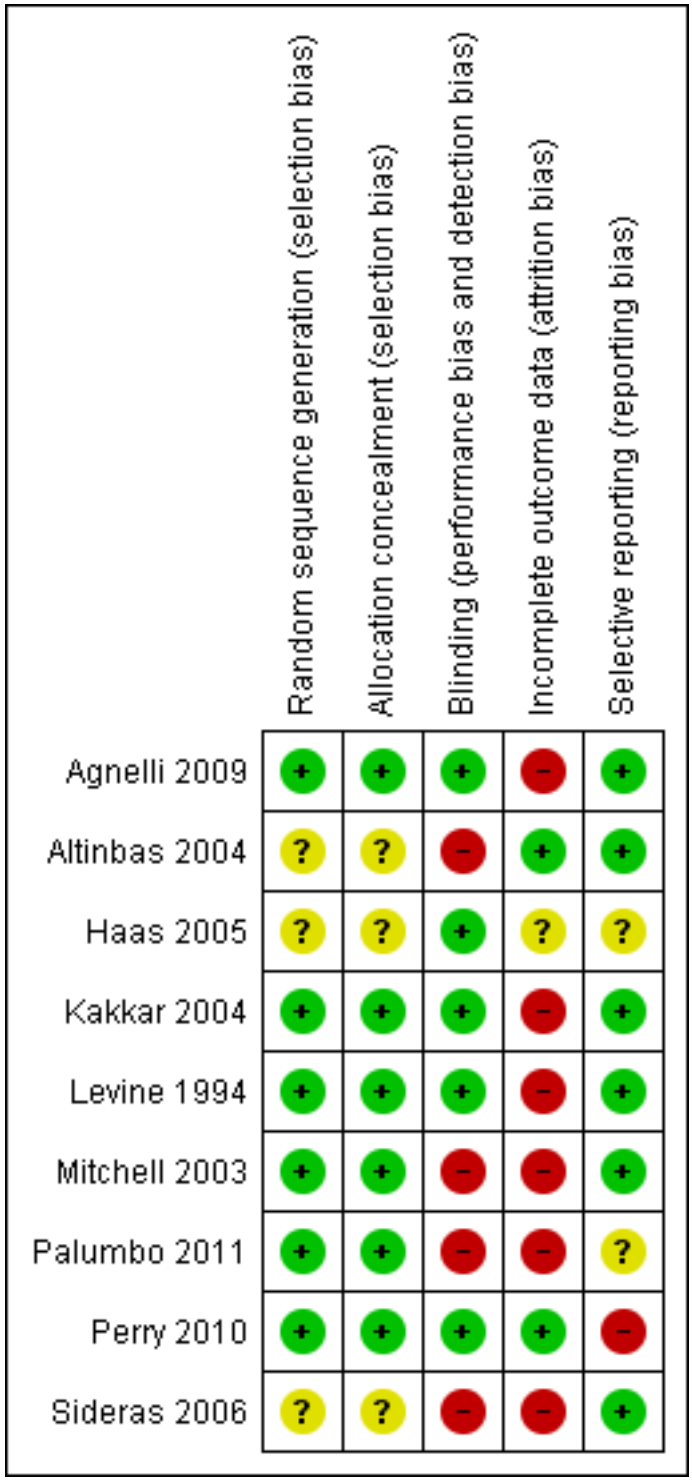
### Excluded studies

The reasons for excluding 16 studies were: other design than a RCT (Meister 2008; Minnema 2004; Paydas 2008); studies on perioperative thromboprophylaxis (Bergqvist 1983; Heilmann 1995; Hills 1972; Macintyre 1974; Maxwell 2000; Sideras 2007; Welti 1981); inclusion of hospitalised cancer patients (Eichinger 2008; Poniewierski 1987; Poniewierski 1988); no relevant outcomes reported (Rajan 1995); no eligible intervention (Klerk 2005); prophylaxis was for catheter-related thrombosis (Kwaan 2007).

## Risk of bias in included studies

The risk of bias in the included studies is shown in Figure 1.

**Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**



### Allocation

Allocation was adequately concealed in six studies included in the meta-analysis (Agnelli 2009; Kakkar 2004; Levine 1994; Mitchell 2003; Palumbo 2011; Perry 2010) and was unclear in the remainder (Altinbas 2004; Haas 2005; Sideras 2006) because the information was not provided.

### Blinding

Five studies had a double-blinded design (Agnelli 2009; Haas 2005; Kakkar 2004; Levine 1994; Perry 2010), three were open.

### Incomplete outcome data

Two studies performed the analysis according to the intention-to-treat principle (Altinbas 2004; Perry 2010) while in five studies the percentages of patients randomised and subsequently excluded from the analysis ranged from 1.3% to 2.8% (Agnelli 2009; Kakkar 2004; Levine 1994; Palumbo 2011; Sideras 2006). The study on paediatric patients used a per protocol analysis and excluded 22% of the patients initially enrolled (Mitchell 2003); it was considered at high risk of bias. The type of analysis and the percentage of patients enrolled and subsequently excluded from the analysis was unclear in the study of Haas 2005.

### Selective reporting

All studies were judged to be free of selective reporting except the study of Perry 2010, which did not report data on the prespecified outcomes of quality of life and cognition assessment. In the study of Palumbo 2011, the number of adverse events was not reported in the final report. For the study of Haas 2005 selective reporting was unclear due to poor reporting.

## Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings table
See: Summary of findings for the main comparison.

#### Anticoagulants versus control

#### LMWH versus inactive control

Based on pooled estimates from six RCTs, LMWH when compared with placebo was associated with a significant reduction in symptomatic VTE (RR 0.62, 95% CI 0.41 to 0.93) which corresponded to a NNT of 60 (Figure 2), in the absence of heterogeneity ($I^2$ = 0%). Funnel plot exploration did not show any evidence of biases associated with small studies (Figure 3). Data suggested a 60% increased risk of major bleeding, albeit this finding was not statistically significant (RR 1.57, 95% CI 0.69 to 3.60) (Figure 4), with low-degree heterogeneity ($I^2$ = 10%) in the absence of funnel plot asymmetry (Figure 5). There was no significant effect on symptomatic PE (RR 0.63, 95% CI 0.21 to 1.91; $I^2$ = 3%) or DVT (RR 0.60, 95% CI 0.33 to 1.07; $I^2$ = 0%). The risk of overall VTE was reduced by 45% (RR 0.55, 95% CI 0.34 to 0.88; $I^2$ = 0%) whereas there was no statistically significant benefit or harm for asymptomatic VTE, minor bleeding, one-year mortality, symptomatic arterial thromboembolism, superficial thrombophlebitis or serious adverse events (Data and analyses). None of the studies considered quality of life, heparin-induced thrombocytopenia or the incidence of osteoporosis as study outcomes.

**Figure 2. Forest plot of comparison: 1 Anticoagulants versus control, outcome: 1.1 Symptomatic VTE for LMWH vs placebo.**

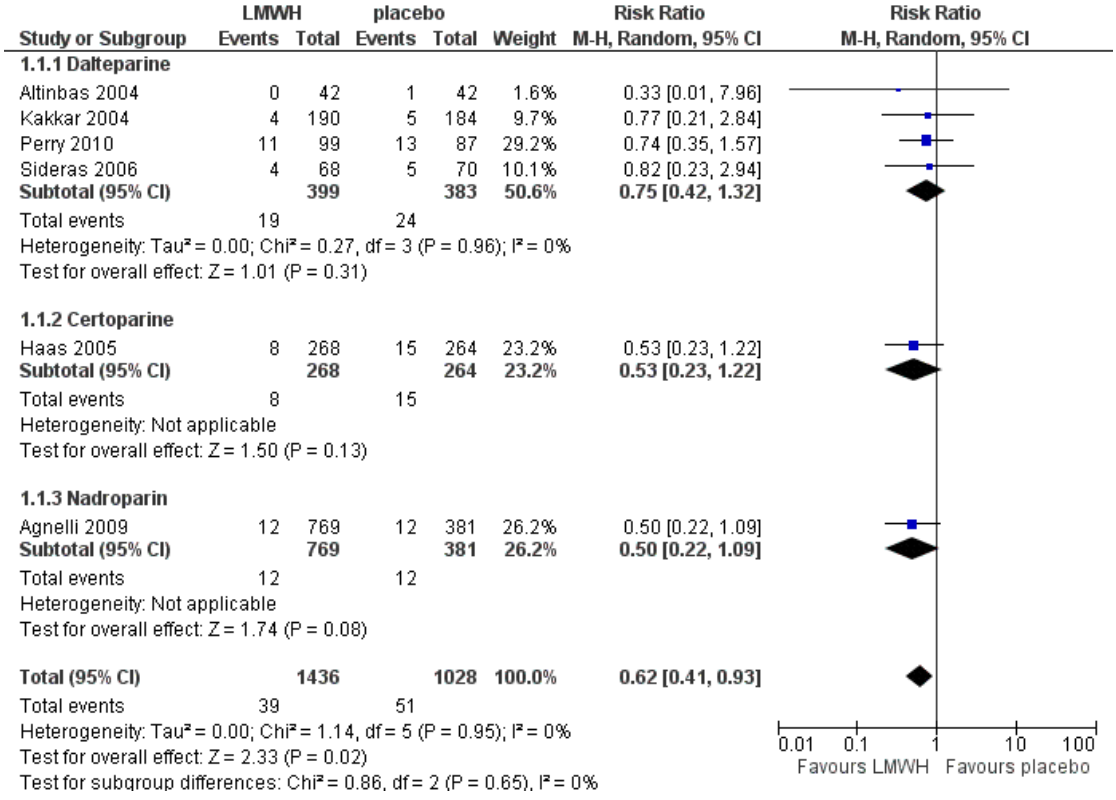


**Figure 3. Funnel plot of comparison: 1 Anticoagulants versus control, outcome: 1.1 Symptomatic VTE for LMWH vs placebo.**

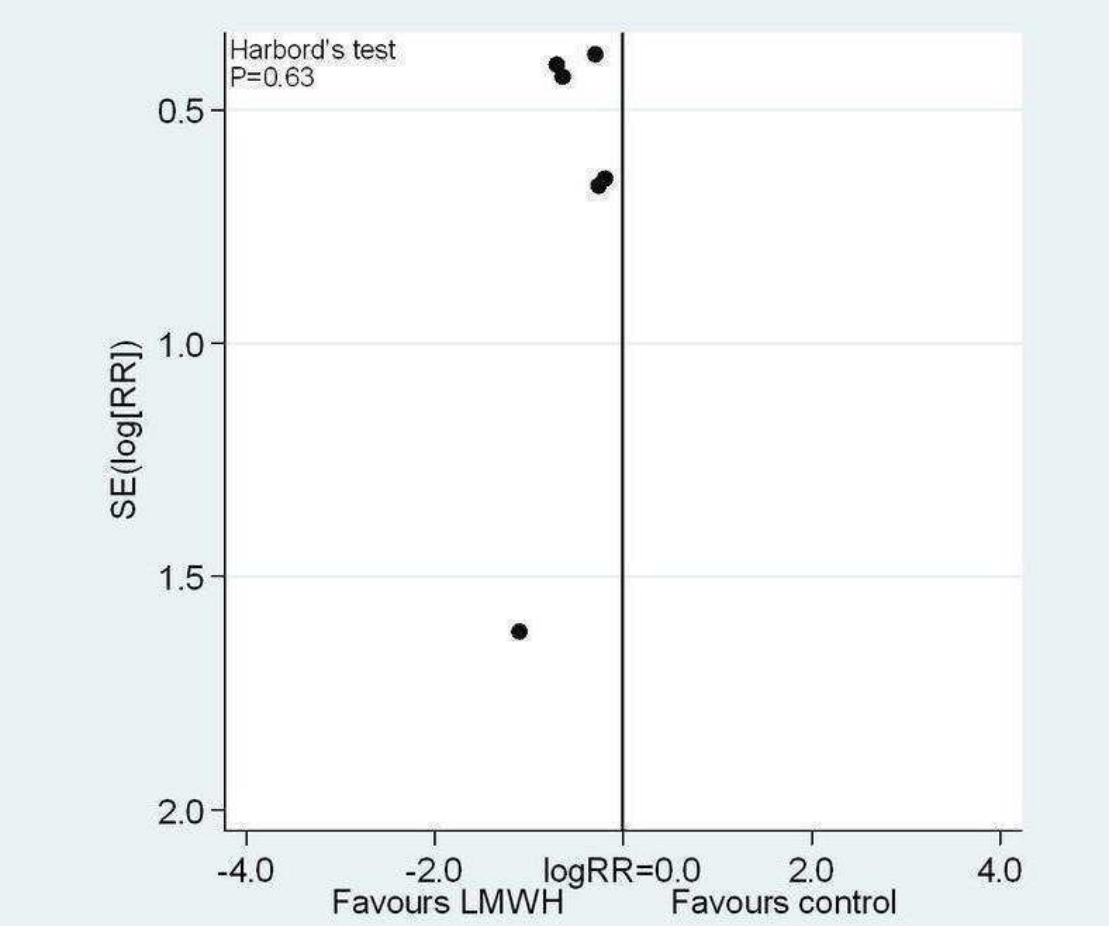


**Figure 4. Forest plot of comparison: 2 Anticoagulants versus control, outcome: 2.1 Major bleeding for LMWH vs placebo.**

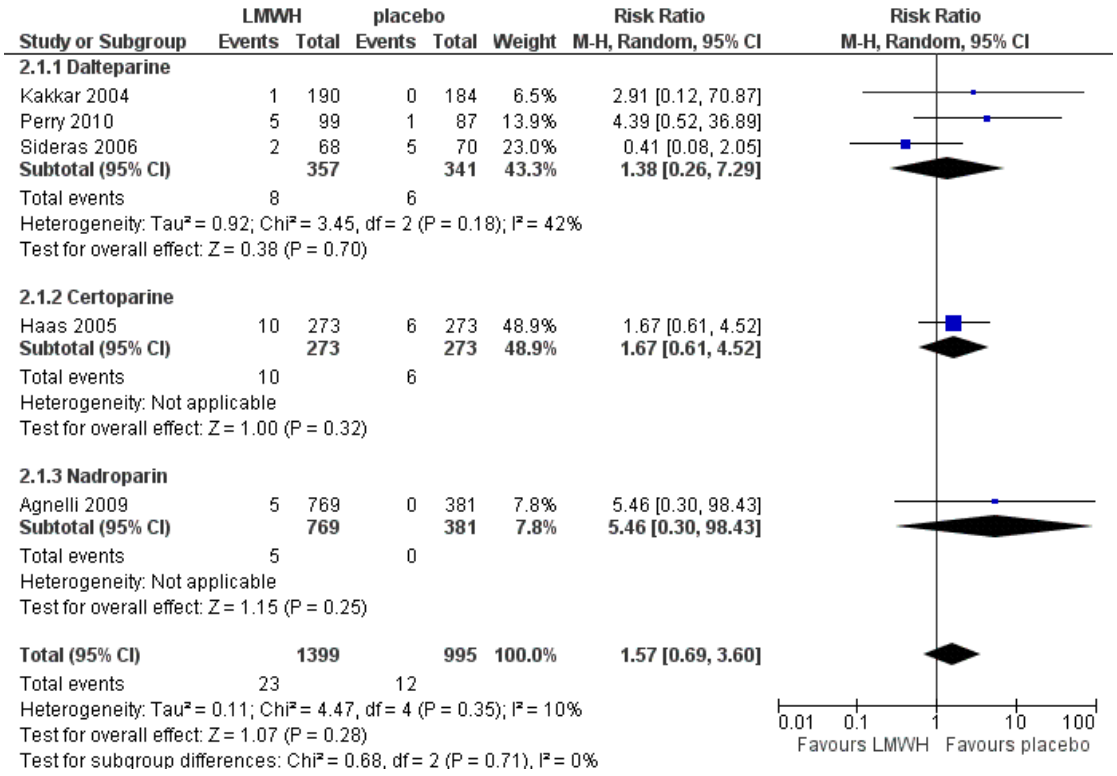
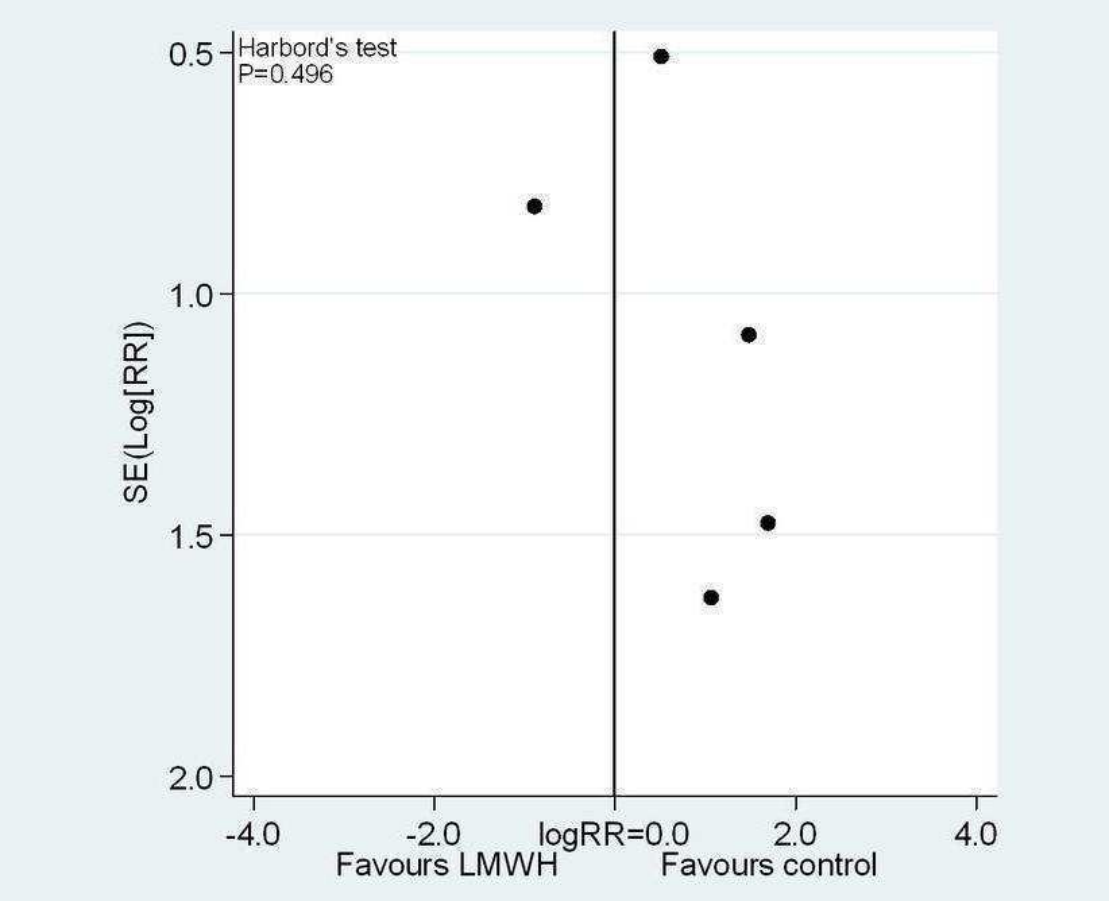


**Figure 5. Funnel plot of comparison: 2 Anticoagulants versus control, outcome: 2.1 Major bleeding for LMWH vs placebo.**




The low-degree heterogeneity for major bleeding was investigated further in stratified analysis. For type of cancer, stage of cancer or differences in the use of co-interventions there was not enough contrast between the trials groups for the analysis. All other pre-specified variables had no significant interaction with the LMWH effect on bleeding (See Table 1). In general, suboptimal design features seemed to be associated with lower effect sizes. For example, when only studies with both adequate sequence generation and allocation concealment were considered (Agnelli 2009; Kakkar 2004; Perry 2010) a four-fold increased risk of major bleeding with LMWH was observed, with a wide confidence interval that crossed the 'no difference' value of 1 (RR 4.25, 95% CI 0.94 to 19.24; P = 0.24).

Three studies reported on symptomatic VTE and major bleeding in patients with non-small cell (Haas 2005) or small cell lung cancer (Altinbas 2004), or both (Agnelli 2009). Pooled analysis of these trials showed a non-significant 46% reduction in symptomatic VTE (RR 0.54, 95% CI 0.27 to 1.09) and a non-significant 73% higher risk of major bleeding with LMWH as compared to the control treatment (RR 1.73, 95% CI 0.65 to 4.57), with no evidence of statistical heterogeneity ($I^2$ = 0%).

**LMWH versus active control**

In the study of Palumbo 2011 LMWH was associated with a 67% reduction in symptomatic VTE relative to warfarin (RR 0.33, 95% CI 0.14 to 0.83) while the difference with aspirin was not statistically significant (RR 0.50, 95% CI 0.19 to 1.31). There were no differences between LMWH, aspirin and warfarin regarding the incidence of major bleeding, symptomatic PE or DVT, minor bleeding and symptomatic arterial thromboembolism.

#### VKA versus inactive control

Levine 1994 reported a trend for a reduction in symptomatic VTE (RR 0.15, 95% CI 0.02 to 1.20) relative to placebo. There was no significant effect on major bleeding (RR 0.52, 95% CI 0.05 to 5.71), symptomatic PE (RR 1.05, 95% CI 0.07 to 16.58), symptomatic DVT (RR 0.08, 95% CI 0.00 to 1.42) or minor bleeding (RR 2.44, 95% CI 0.64 to 9.27). No symptomatic arterial thromboembolic events were observed in the VKA or placebo groups.

#### VKA versus active control

Palumbo 2011 reported a non-statistically significant difference between VKA and aspirin (RR 1.50, 95% CI 0.74 to 3.04). We refer to the previous section for the description of the comparison of VKA with LMWH.

#### Antithrombin versus inactive control

Antithrombin was assessed in one study that recruited paediatric patients (Mitchell 2003). The effects of antithrombin on symptomatic VTE (RR 0.84, 95% CI 0.41 to 1.73) and major bleeding (RR 0.78, 95% CI 0.03 to 18.57) were not statistically significant.

## DISCUSSION

### Summary of main results

The use of LMWH as primary thromboprophylaxis in ambulatory cancer patients receiving chemotherapy is associated with a 40% reduction in symptomatic VTE. Data suggested a non-statistically significant 60% higher risk of major bleeding, but confidence intervals were wide and thus the finding inconclusive. The available data did not show any statistically significant effect of LMWH on PE or mortality, and no study reported on thrombocytopenia or osteoporosis. The lack of a placebo or non-active control group does not allow firm judgements about the efficacy and safety of LMWH in myeloma patients. The effect of warfarin on symptomatic VTE was not statistically significant and antithrombin was evaluated in a relatively small study involving paediatric patients. None of the included RCTs tested UFH, fondaparinux, direct factor Xa inhibitors or mechanical interventions.

### Quality of the evidence

Our systematic approach to searching, study selection and data extraction followed that of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2003). The methodological quality of the included studies varied from low to high, see Summary of findings for the main comparison and Figure 1. An inspection of the funnel plot and formal analysis of asymmetry did not indicate asymmetry for primary efficacy and safety outcomes (see Figure 3; Figure 5).

### Potential biases in the review process

Our systematic approach and the consistency of the results (lack of significant heterogeneity) increase the confidence in the internal validity of our findings. One limitation of this review is that the 'no difference' findings may be related to the small number of RCTs and small number of studied patients and of events, as well as the absence of a true effect. In this regard, the non-significant association between LMWH use and major bleeding events could indeed be the result of the relatively low number of events observed across the studies. Another limitation related to the small number of RCTs was our inability to conduct subgroup analyses for the primary efficacy outcome by exploring the impact on the treatment effect of age (below 65 years versus above 65 years); type of cancer, stage of cancer (metastatic versus non-metastatic); concealment of allocation (adequate versus inadequate or unclear); blinding (adequate versus inadequate or unclear); analysis in accordance with the intention-to-treat principle (yes versus no or unclear); trial size; and differences in the use of co-interventions in the trial groups. The lack of reporting as well as the heterogeneity of cancers treated did not allow us to assess the importance of background chemotherapy on the response to thromboprophylaxis.

### Agreements and disagreements with other studies or reviews

The evidence on the use of thromboprophylaxis in ambulatory cancer patients receiving chemotherapy was recently summarised by the American Society of Clinical Oncology (Rana 2009). Relative to that narrative review, we included five additional studies (Altinbas 2004; Kakkar 2004; Mitchell 2003; Palumbo 2011; Sideras 2006). Three of these studies evaluated the effects of prophylactic doses of LMWH on survival as the primary outcome while reporting VTE events as secondary outcomes (Altinbas 2004; Kakkar 2004; Sideras 2006). Although the focus was not on VTE and some cases may have been under-diagnosed, the overall incidence of symptomatic VTE was comparable with the other studies included in the review. Overall, the main conclusions of Rana 2009 are substantially in line with our findings and do not support the widespread use of primary thromboprophylaxis in ambulatory cancer patients. The pooled estimates provided in the present meta-analysis underline the need for additional studies to confirm the benefit of prophylaxis on 'hard' outcomes such as symptomatic PE, but also to exclude a significant increase in major bleeding with LMWH.

## AUTHORS' CONCLUSIONS

### Implications for practice

When deciding whether to use primary antithrombotic prophylaxis in ambulatory cancer patients receiving chemotherapy, a clinician needs to determine the patients' baseline risk of VTE and weigh the magnitude of benefit, especially on clinically major endpoints, with antithrombotic prophylaxis against the risk of bleeding. LMWH was associated with a 40% lower incidence of symptomatic VTE. Albeit not statistically significant, the rate of symptomatic PE was reduced to a similar extent. LMWH was associated with a 60% increase in major bleeding when compared with inactive control but the confidence interval was wide and crossed the line of no difference. This finding could still be the result of the relatively small size of the population or low number of events (type II error). Co-morbidities predisposing to bleeding, which often represent an exclusion criterion in randomised controlled studies on anticoagulants, might result into higher major bleeding complications and limit the use of thromboprophylaxis in 'real life'. An additional concern may be the use of thromboprophylaxis in some types of cancers, such as those in the brain, which are considered to be at risk for major bleeding. Thus, despite the encouraging results of this review, routine prophylaxis in ambulatory cancer patients cannot be recommended before safety issues are adequately addressed. Specific patients subgroups that might benefit from prophylaxis cannot be specified.

### Implications for research

Future studies are needed to clearly establish the risk to benefit ratio of anticoagulants in ambulatory cancer patients receiving chemotherapy and to identify subgroups which may benefit most from thromboprophylaxis. Moreover, evidence-based bleeding risk assessment scores may help in selecting subgroups at lower risk of bleeding complications. Research is needed to evaluate the effects of newer anticoagulants such as direct Xa inhibitors and direct thrombin inhibitors, which have shown promise compared to heparin or vitamin K antagonists in other settings.

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* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

**Agnelli 2009**

| | |
|---|---|
| Methods | Prospective, multicentre RCT; modified intention-to-treat analysis |
| Participants | Ambulatory patients older than 18 years of age who were receiving chemotherapy for metastatic or locally advanced lung, gastrointestinal, pancreatic, breast, ovarian, or head and neck cancer. Age: 62.1 years in the nadroparin group; 63.7 years in the placebo |
| Interventions | Nadroparin (3800 IU anti-Xa sc, od)<br>Control: placebo<br>Study treatment started on the same day as chemotherapy (the first cycle or a new course) , and given for the duration of chemotherapy or up to a maximum of 120 days (±10 days) |
| Outcomes | Primary outcomes:<br>1) composite of symptomatic venous or arterial thromboembolic events occurring during the study treatment plus 10 days<br>2) major bleeding that occurred between randomisation and 48 h after the last injection of the study drug<br>Secondary efficacy outcomes: asymptomatic thromboembolic events incidentally diagnosed, survival at the end of study treatment and at 12 months, superficial thrombophlebitis of the lower limbs, response to chemotherapy, central venous catheter-related complications of possible thrombotic origin<br>Secondary safety outcome: minor bleeding |
| Notes | Antiplatelet agents, oral anticoagulants, fibrinolytic agents, unfractionated heparin or low molecular weight heparin other than nadroparin not allowed during the study period |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Web-based system |
| Allocation concealment (selection bias) | Low risk | Web-based system |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Double blinding |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Percentage of patients enrolled and subsequently excluded from the analysis: 1.4% (16/1166) |

**Agnelli 2009** (*Continued*)

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Low risk | The report includes all expected outcomes |

**Altinbas 2004**

| | |
|---|---|
| Methods | RCT; intention-to-treat analysis |
| Participants | Patients between ages 18 and 75 years with histologically confirmed small cell lung carcinoma with an Eastern Cooperative Oncology Group performance status of less than 3 and normal hematological, renal and hepatic function tests. Median age: 58 years (range 34-75) |
| Interventions | Dalteparin (5000 IU sc, od)<br>Control: no dalteparin<br>Dalteparin stopped with disease progression or at the end of the 18 weeks of chemotherapy |
| Outcomes | Primary outcome: overall survival<br>Secondary outcomes: progression-free survival, side-effects |
| Notes | |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No information provided |
| Allocation concealment (selection bias) | Unclear risk | No information provided |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Open study |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Percentage of patients enrolled and subsequently excluded from the analysis: 0% |
| Selective reporting (reporting bias) | Low risk | The report includes all expected outcomes |

**Haas 2005**

| | |
|---|---|
| Methods | RCT |
| Participants | Patients with advanced breast cancer (n = 353) or non-small cell lung carcinoma (n = 547) who received chemotherapy |

**Haas 2005** (*Continued*)

| | | |
|---|---|---|
| Interventions | Certoparin (3000 IU sc, od) for 6 months<br>Control: placebo | |
| Outcomes | Primary outcomes: symptomatic VTE and asymptomatic DVT<br>Secondary outcomes: major bleeding | |
| Notes | | |
| ***Risk of bias*** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | No information provided in the abstract |
| Allocation concealment (selection bias) | Unclear risk | No information provided in the abstract |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Double blinding |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | No information provided in the abstract |
| Selective reporting (reporting bias) | Unclear risk | No information provided in the abstract |

**Kakkar 2004**

| | |
|---|---|
| Methods | Prospective, multicentre RCT; intention-to-treat analysis |
| Participants | Patients of 18 and 80 years with histologically confirmed advanced stage III or IV (locally advanced or metastatic) malignant disease of the breast, lung, gastrointestinal tract, pancreas, liver, genitourinary tract, ovary, or uterus. Age: 62 years in the dalteparin group and 60.9 years in the placebo |
| Interventions | Dalteparin (5.000 IU sc, od)<br>Control: placebo (0.9% normal saline).<br>Study treatment given for 1 year or until the patient died, whichever occurred sooner |
| Outcomes | Primary outcomes: mortality after 1 year of therapy<br>Secondary outcomes:symptomatic, objectively confirmed VTE disease and bleeding complications |
| Notes | |
| ***Risk of bias*** | |

**Kakkar 2004** (*Continued*)

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Web-based system |
| Allocation concealment (selection bias) | Low risk | Web-based system |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Double blinding |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Percentage of patients enrolled and subsequently excluded from the analysis: 2.8% (11/385) |
| Selective reporting (reporting bias) | Low risk | The report includes all expected outcomes |

**Levine 1994**

| | |
|---|---|
| Methods | Prospective, multicentre RCT; intention-to-treat analysis |
| Participants | Patients with metastatic stage IV breast carcinoma who had been receiving first-line or second-line chemotherapy for 4 weeks or less. Mean age: 57 years in the warfarin group and 56 years in the placebo |
| Interventions | Warfarin (1 mg daily for 6 weeks and then adjusted to maintain the INR between 1.3 to 1.9)<br>Control: placebo<br>Study treatment began either at the start of chemotherapy or within the next 4 weeks and continued until 1 week after termination of chemotherapy |
| Outcomes | Primary outcomes:<br>1) VTE and arterial thrombosis<br>2) major and minor bleeding<br>Secondary outcomes: survival |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Web-based system |
| Allocation concealment (selection bias) | Low risk | Web-based system |

**Levine 1994** (*Continued*)

| | | |
|---|---|---|
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Double blinding |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Percentage of patients enrolled and subsequently excluded from the analysis: 1.3% (4/315) |
| Selective reporting (reporting bias) | Low risk | The report includes all expected outcomes |

**Mitchell 2003**

| | |
|---|---|
| Methods | Prospective RCT; per protocol analysis |
| Participants | Paediatric patients newly diagnosed with acute lymphoblastic leukaemia treated with L-asparaginase and a functioning central venous line placed within 2 weeks of initiating induction chemotherapy |
| Interventions | Thrombate III (infusions once weekly for 4 weeks to increase plasma concentrations of antithrombin to approximately 3.0 units/mL but no more than 4.0 units/mL)<br>Control: standard care |
| Outcomes | Primary outcomes:<br>1) clinically symptomatic or asymptomatic thrombotic event in any location<br>2) major and minor bleeding<br>Secondary outcomes: surrogate outcome for thrombotic events by measuring markers of thrombin generation |
| Notes | Patients did receive small amounts of UFH for prophylaxis of central venous line-blockage either by continuous infusion (1-3 units/mL) or intermittent flushes (50-100 units/mL up to 4 times per day) according to local standard of care |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Web-based system |
| Allocation concealment (selection bias) | Low risk | Web-based system |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Open study |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Percentage of patients enrolled and subsequently excluded from the analysis: 22% (24/109) |

**Mitchell 2003** (*Continued*)

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Low risk | The report includes all expected outcomes |

**Palumbo 2011**

| | |
|---|---|
| Methods | Randomised, open-label, multicentre study, intention-to-treat analysis |
| Participants | Patients with previously untreated myeloma who received thalidomide-containing regimens and had no clinical indication or contraindication for a specific antiplatelet or anticoagulant therapy. Median age: aspirin 61 years (55 - 66), warfarin 60 years (54 - 66), heparin 62 years (55 - 66) |
| Interventions | Aspirin (100 mg/d), low-dose warfarin (1.25 mg/d), or LMWH (enoxaparin 40 mg/d). The prophylaxis was administered during the three cycles of induction therapy in patients ≤ 65 years and during the first six cycles of induction therapy in patients > 65 years |
| Outcomes | Primary endpoint:<br>a composite measure of a first episode of objectively confirmed symptomatic DVT, PE, arterial thrombosis, acute myocardial infarction or stroke, or sudden, otherwise unexplained death during the first 6 months from random assignment<br>Secondary endpoints:<br>-each component of the composite primary end point<br>-long-term cumulative incidence of the primary end point<br>-major and minor bleeding events<br>-any toxicity that required interruption of study prophylaxis |
| Notes | Karnofsky performance status <70%: aspirin 25%, warfarin 29%, heparin 30% |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random assignment sequence was generated by a centralised computer |
| Allocation concealment (selection bias) | Low risk | Patients randomly allocated to treatments using an automated assignment procedure concealed to the investigators |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Open study |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Percentage of patients enrolled and subsequently excluded from the analysis: 1.36% (9/659) |

**Palumbo 2011** (*Continued*)

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Unclear risk | The number of adverse events in the treatment groups not reported in the final report |

**Perry 2010**

| | |
|---|---|
| Methods | Prospective, multicentre RCT; intention-to-treat analysis |
| Participants | Patients over 18 years of age with newly diagnosed, pathologically confirmed WHO Grade 3 or Grade 4 glioma |
| Interventions | Dalteparin (5000 IU sc, od)<br>Control: placebo<br>Study treatment given for 6 months starting within the first month after surgery. Patients allowed to continue study medication for 12 months |
| Outcomes | Primary outcomes: objectively documented symptomatic DVT or PE occurring during the six months post-randomisation<br>Secondary outcomes: major and all bleeding, quality of life, cognition assessments, and death |
| Notes | |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Web-based system |
| Allocation concealment (selection bias) | Low risk | Web-based system |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Double blinding |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Percentage of patients enrolled and subsequently excluded from the analysis: 0% (0/186) |
| Selective reporting (reporting bias) | High risk | The outcomes quality of life and cognition assessment not reported in the final report |

**Sideras 2006**

| | |
|---|---|
| Methods | RCT |
| Participants | Patients with advanced breast cancer who failed first-line chemotherapy, advanced prostate cancer who failed primary hormonal therapy, advanced lung cancer, or advanced colorectal cancer |
| Interventions | *First part of the study, double blinded (52 patients):*<br>Dalteparin (5000 IU sc, od) plus standard clinical care<br>Control: placebo (saline injections) plus standard clinical care<br>*Second part of the study, open (86 patients)*<br>Dalteparin (5000 IU sc, od) plus standard clinical care<br>Control: standard clinical care alone.<br>Duration: 18 weeks or until disease progression |
| Outcomes | Primary outcome: overall survival<br>Secondary outcomes: toxic effects, incidence of thromboembolic events, changes in quality of life |
| Notes | |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No information provided |
| Allocation concealment (selection bias) | Unclear risk | No information provided |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Double blinding in the first part of the trial, open in the second part |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Percentage of patients enrolled and subsequently excluded from the analysis: 2.1% (3/141) |
| Selective reporting (reporting bias) | Low risk | The report includes all expected outcomes |

od: once daily
sc: subcutaneous

## Characteristics of excluded studies *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| Bergqvist 1983 | Perioperative thromboprophylaxis |
| Eichinger 2008 | Inadequate population: hospitalised cancer patients |
| Heilmann 1995 | Perioperative thromboprophylaxis |
| Hills 1972 | Perioperative thromboprophylaxis |
| Klerk 2005 | Inadequate intervention, not primary thromboprophylaxis |
| Kwaan 2007 | Prophylaxis for catheter-related thrombosis |
| Macintyre 1974 | Perioperative thromboprophylaxis |
| Maxwell 2000 | Perioperative thromboprophylaxis |
| Meister 2008 | Not a RCT |
| Minnema 2004 | Not a RCT |
| Paydas 2008 | Not a RCT |
| Poniewierski 1987 | Inadequate population: hospitalised cancer patients |
| Poniewierski 1988 | Inadequate population: hospitalised cancer patients |
| Rajan 1995 | Inadequate outcomes |
| Sideras 2007 | Perioperative thromboprophylaxis |
| Welti 1981 | Perioperative thromboprophylaxis |

## Characteristics of studies awaiting assessment *[ordered by study ID]*

**Salat 1990**

| | |
|---|---|
| Methods | Prospective RCT |
| Participants | Patients (n = 80) with malignant diseases |
| Interventions | Unfractionated heparin (2 x 7500 IU/mL)<br>Control: dalteparin (5000 IU sc, od) |

**Salat 1990** (*Continued*)

| | |
|---|---|
| Outcomes | Thrombosis and haemorrhagic complications |
| Notes | |

od: once daily
sc: subcutaneous

## Characteristics of ongoing studies *[ordered by study ID]*

**Anon 2006**

| | |
|---|---|
| Trial name or title | A randomised, double-blind, placebo-controlled study of apixaban for the prevention of thromboembolic events in patients undergoing treatment for advanced cancer: a phase II pilot study |
| Methods | Unclear methods of randomisation, allocation concealment and analysis; double blinded |
| Participants | Patients with advanced or metastatic cancer receiving chemotherapy ≥ 90 days entering the study within six weeks from the start of chemotherapy |
| Interventions | Apixaban (5 mg oral, qd)<br>Control: placebo<br>Study treatment given for 12 weeks |
| Outcomes | Primary outcome: fatal or non-fatal major bleeding or a clinically relevant non-major bleeding event during the treatment period<br>Secondary outcome: symptoms compatible with VTE during the treatment and 30 day follow-up periods |
| Starting date | June 2006 |
| Contact information | Bristol-Myers Squibb |
| Notes | |

**Francis 2009**

| | |
|---|---|
| Trial name or title | A prospective randomised multicentre study of dalteparin prophylaxis in high-risk ambulatory cancer patients |
| Methods | Unclear methods of randomisation, allocation concealment and analysis; open label |
| Participants | Patients with a histologic diagnosis of malignancy, planned initiation of a new systemic chemotherapy regimen, and a risk score for VTE ≥ 3 |
| Interventions | Dalteparin (5000 IU sc, od)<br>Control: no dalteparin |

**Francis 2009** (*Continued*)

| | |
|---|---|
| Outcomes | Primary outcome: safety and efficacy of prophylaxis with dalteparin compared to no treatment in reducing VTE<br>Secondary outcome: value of tissue factor as a predictive marker for VTE |
| Starting date | July 2009 |
| Contact information | Francis C |
| Notes | |

**Griffiths 2009**

| | |
|---|---|
| Trial name or title | FRAGMATIC: A randomised phase III clinical trial investigating the effect of fragmin added to standard therapy in patients with lung<br>cancer |
| Methods | Central randomisation using the method of minimisation and stratifying patients for a number of factors; open-label, planned intention-to-treat analysis |
| Participants | Patients with histopathological or cytological diagnosis of primary bronchial carcinoma (small cell or non-small cell) within the last 6 weeks, age 18 or over, ECOG Performance status 0 to 3 |
| Interventions | Dalteparin (5000 IU sc, od) plus standard anticancer treatment; dalteparin is given for 24 weeks and started as soon as possible and before first definitive anticancer treatment<br>Control: standard anticancer treatment |
| Outcomes | Primary outcome: overall survival<br>Secondary out comes: venous thrombotic event free survival, serious adverse events, metastasis-free survival, toxicity, quality of life, breathlessness, anxiety and depression, cost effectiveness, cost utility |
| Starting date | |
| Contact information | Griffiths GO: griffithsg@cardiff.ac.uk |
| Notes | |

**Levin 2008**

| | |
|---|---|
| Trial name or title | A randomised phase II trial of aspirin for primary prophylaxis of VTE in glioblastoma |
| Methods | Unclear methods of randomisation, allocation concealment and analysis; double blinded |
| Participants | Patients with histologically proven supratentorial malignant WHO grade IV gliomas documented on magnetic resonance imaging or computed tomography, Karnofsky performance status $\geq$ 60 at study entry, no more than 16 weeks from the diagnosis of glioblastoma |

**Levin 2008** (*Continued*)

| | |
|---|---|
| Interventions | Aspirin (325 mg oral, od)<br>Control: placebo |
| Outcomes | Primary outcome: VTE<br>Secondary outcomes: clinical and laboratory factors which are associated with increased risk of VTE |
| Starting date | November 2008 |
| Contact information | Levin VA |
| Notes | |

**Liebman 2009**

| | |
|---|---|
| Trial name or title | Apixaban in patients with metastatic cancer: a randomised phase II feasibility study |
| Methods | Unclear methods of randomisation, allocation concealment, analysis. Double blinding |
| Participants | Patients with metastatic cancer on first or second-line chemotherapy |
| Interventions | Apixaban 5, 10, or 20 mg/day<br>Comparator: placebo<br>Duration of treatment: 12 weeks |
| Outcomes | Major bleeding, clinically relevant non-major bleeding, VTE, grade > 3 adverse events |
| Starting date | Not available from the abstract |
| Contact information | Liebman H |
| Notes | |

**Maraveyas 2003**

| | |
|---|---|
| Trial name or title | A phase II randomised study of chemo-anticoagulation (Gemcitabine-Dalteparin) vs chemotherapy alone (Gemcitabine) for locally advanced and metastatic pancreatic adenocarcinoma |
| Methods | Multicentre randomised controlled trial |
| Participants | Participants with:<br>1. Histologically or cytologically confirmed metastatic or locally advanced adenocarcinoma of the pancreas (patients with clinical 'high probability' of pancreatic cancer and biopsy suggestive but not diagnostic of pancreatic cancer may be eligible based on review by the principal investigator)<br>2. Measurable or evaluable disease<br>3. Karnofsky performance status (PS) 60-100% OR WHO PS 0-2<br>4. Life expectancy > 12 weeks<br>5. Absolute neutrophil count > 2,000/mm$^3$ |

**Maraveyas 2003** (*Continued*)

| | |
|---|---|
| | 6. WBC > 3,000/mm³<br>7. Platelet count > 100,000/mm³<br>8. Creatinine clearance > 50 mL/min<br>9. INR ≤ 1.5 times upper limit of normal (ULN)<br>10. Bilirubin < 1.5 times ULN (stent allowed)<br>11. Adequate contraceptive measures in place |
| Interventions | Patients are stratified according to disease progression (locally advanced vs metastatic) and Karnofsky performance status (≥80% vs < 80%), then randomised to 1 of 2 treatment arms:<br>Arm I: Patients receive gemcitabine hydrochloride IV over 30 minutes once weekly in weeks 1-7 and 9-11.<br>Arm II: Patients receive LMWH dalteparin sc od in weeks 1-12. Patients also receive gemcitabine hydrochloride as in Arm I |
| Outcomes | Primary outcome: Incidence of VTE reduction<br>Secondary outcomes:<br>1. Early survival benefits<br>2. Toxicity<br>3. Overall survival<br>4. Time to disease progression<br>5. Effect of drug combination on serological markers of thromboangiogenesis |
| Starting date | 06/01/2003 |
| Contact information | Maraveyas A - mdsam@doctors.org.uk |
| Notes | Data of a substudy on molecular markers only was published in May 2010 (Blood Coagulation and Fibrinolysis 2010;21(5):452-8) |

**Oettle 2004**

| | |
|---|---|
| Trial name or title | A prospective, randomised trial of simultaneous pancreatic cancer treatment with enoxaparin and chemotherapy |
| Methods | Unclear methods of randomisation, allocation concealment, analysis, and blinding |
| Participants | Patients of 18 years or older with histologically or cytologically proven advanced pancreatic cancer stage Iva, b, no previous tumour specific therapy of the main tumour or distant metastases, Karnofsky performance status greater than 50%, measurable disease visible per computed tomography or magnetic resonance tomography not older than 14 days, no previous DVT of the legs within last two years, leucocytes greater than 3.5 x 10^9/L, platelets greater than 100 x 10^9/L |
| Interventions | Patients with Karnofsky performance status greater than 80% and normal kidney function:<br>Enoxaparin (1 mg/kg sc, od) plus gemcitabine, cisplatin, 5-fluorouracil and folinic acid<br>Control: gemcitabine, cisplatin, 5-fluorouracil and folinic acid<br><br>Patients with Karnofsky performance status less than 80% and increased creatinine plasma levels (greater than 1.3 mg/dl):<br>Enoxaparin (1 mg/kg sc, od) plus gemcitabine |

**Oettle 2004** (*Continued*)

| | |
|---|---|
| | Control: gemcitabine |
| Outcomes | Primary outcome: thromboembolic events<br>Secondary outcomes<br>1. Thromboembolic rate at time points 6, 9 and 12 months<br>2. Time to progression<br>3. Overall survival, progression-free survival<br>4. Rate of remission, duration of remission<br>5. Toxicity: National Cancer Institute Common Toxicity Criteria grade differentiation<br>6. Quality of life |
| Starting date | April 2004 |
| Contact information | Oettle H |
| Notes | |

**Riess 2008**

| | |
|---|---|
| Trial name or title | Rationale and design of PROSPECT-CONKO 004: a prospective, randomised trial of simultaneous pancreatic cancer treatment with enoxaparin and chemotherapy |
| Methods | Prospective, open-label, randomised, phase IIb study |
| Participants | Patients of 18 years or older with histologically or cytologically confirmed locally advanced or metastasised pancreatic cancer who are treated with a palliative chemotherapy using either gemcitabine alone or in combination with cisplatin, 5-fluorouracil and folinic acid, who have not received previous radio- or chemotherapy of the primary tumour or the reference lesions; and who have Karnofsky performance status $\geq$ 60%; measurable tumour lesion confirmed by computed tomography or magnetic resonance tomography within the last 14 days; no DVT within the last two years, leucocytes greater than 3.5 x 10^9/L, thrombocytes $\geq$ 100 x 10^9/L |
| Interventions | Enoxaparin (1 mg/kg sc, qd for the first three months followed by 40 mg qd for an additional three months) plus standard anticancer treatment<br>A reduction of enoxaparin to 0.5 mg/kg is recommended if thrombocytes are between 50,000 and 75,000/$\mu$l until an increase in thrombocytes > 75,000/$\mu$l. Enoxaparin is to be interrupted in thrombocytopenia below 50,000/$\mu$l<br>Control: standard anticancer treatment |
| Outcomes | Primary outcome: clinically relevant VTE within the first three months<br>Secondary outcomes: symptomatic and asymptomatic VTE after 6, 9 and 12 months; remission at 3, 6, 9 and 12 months, overall survival, rates of remission at 3, 6, 9 and 12 months, toxicity of the therapeutic regimen, time to tumour regression and quality of life during chemotherapy with or without enoxaparin and the rate of major bleeding |
| Starting date | |
| Contact information | Hanno Riess - hanno.riess@charite.de |

**Riess 2008** (*Continued*)

| | |
|---|---|
| Notes | |

**Turpie 2008**

| | |
|---|---|
| Trial name or title | A multinational, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of AVE5026 in the prevention of VTE in cancer patients at high risk for VTE and who are undergoing chemotherapy |
| Methods | Randomised, double-blind, placebo-controlled |
| Participants | Patients with metastatic or locally advanced solid tumours of lung, pancreas, stomach, colon/rectum, bladder or ovary initiating a (new) course of chemotherapy with a minimum intent of three months therapy |
| Interventions | AVE5026 (sc, od)<br>Control: placebo |
| Outcomes | Primary outcome: time-to-first occurrence of symptomatic DVT of lower or upper limbs, non-fatal PE, and VTE-related deaths from randomisation up to three calendar days after last study drug injection<br>Secondary outcomes: individual components of the primary outcome measure from randomisation up to three calendar days after last study drug injection; bleedings, transfusions, laboratory data, adverse events, deaths during study period |
| Starting date | June 2008 |
| Contact information | Turpie A |
| Notes | |

**Vadhan-Raj 2010**

| | |
|---|---|
| Trial name or title | Randomised clinical trial of dalteparin for primary VTE prophylaxis in pancreatic cancer patients undergoing chemotherapy treatment |
| Methods | Unclear methods of randomisation, allocation concealment and analysis; open label |
| Participants | Patients 18 years or older with a diagnosis of advanced stage (unresectable or metastatic) adenocarinoma of the pancreas planning to initiate systemic chemotherapy within two weeks, ECOG performance status 0 - 2, adequate renal function (creatinine clearance of > 50 mL/min) |
| Interventions | Dalteparin (5000 IU sc, od) for 16 weeks<br>Control: no dalteparin |
| Outcomes | Primary outcome: venous thromboembolic events during 16 weeks of treatment |
| Starting date | April 2010 |

**Vadhan-Raj 2010** (*Continued*)

| | |
|---|---|
| Contact information | Vadhan-Raj S |
| Notes | |

**Zwicker 2009**

| | |
|---|---|
| Trial name or title | A randomised controlled trial of enoxaparin thromboprophylaxis in cancer patients with elevated tissue factor bearing microparticles |
| Methods | Unclear methods of randomisation, allocation concealment and analysis; open label |
| Participants | Patients 18 year old or older with histologically confirmed adenocarcinoma of the pancreas (locally advanced or metastatic), colon (stage IV), or lung (unresectable stage III or IV ) and for which standard curative therapies do not exist., who receive first or second line therapy (within 4 weeks of initiating therapy), life expectancy of greater than six months, ECOG performance status 0, 1, or 2 (Karnofsky 60% or greater) |
| Interventions | Enoxaparin (sc od) for six months<br>Control: B and C (high and low tissue factor bearing microparticles): no enoxaparin |
| Outcomes | Primary outcome: VTE events during three years<br>Secondary outcomes: major bleeding, overall survival, symptomatic or proximal VTE events at six months, cumulative incidence of total VTE events in cancer patients with low tissue factor bearing microparticles compared with those with high tissue factor bearing microparticles not treated with enoxaparin, influence of chemotherapy or enoxaparin on tissue factor bearing microparticles levels, association between absolute tissue factor bearing microparticles levels and thrombotic risk |
| Starting date | May 2009 |
| Contact information | Zwicker J |
| Notes | |

od: once daily
qd: four times daily
sc: subcutaneous

## DATA AND ANALYSES

### Comparison 1. Anticoagulants versus control: symptomatic VTE

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Symptomatic VTE: LMWH vs placebo | 6 | 2464 | Risk Ratio (M-H, Random, 95% CI) | 0.62 [0.41, 0.93] |
| 1.1 Dalteparine | 4 | 782 | Risk Ratio (M-H, Random, 95% CI) | 0.75 [0.42, 1.32] |
| 1.2 Certoparine | 1 | 532 | Risk Ratio (M-H, Random, 95% CI) | 0.53 [0.23, 1.22] |
| 1.3 Nadroparin | 1 | 1150 | Risk Ratio (M-H, Random, 95% CI) | 0.50 [0.22, 1.09] |
| 2 Symptomatic VTE: LMWH vs aspirin | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3 Symptomatic VTE: LMWH vs warfarin | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 4 Symptomatic VTE: vitamin K antagonists vs placebo | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 5 Symptomatic VTE: warfarin vs aspirin | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 6 Symptomatic VTE: antithrombin vs placebo | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

### Comparison 2. Anticoagulants versus control: major bleeding

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Major bleeding: LMWH vs placebo | 5 | 2394 | Risk Ratio (M-H, Random, 95% CI) | 1.57 [0.69, 3.60] |
| 1.1 Dalteparine | 3 | 698 | Risk Ratio (M-H, Random, 95% CI) | 1.38 [0.26, 7.29] |
| 1.2 Certoparine | 1 | 546 | Risk Ratio (M-H, Random, 95% CI) | 1.67 [0.61, 4.52] |
| 1.3 Nadroparin | 1 | 1150 | Risk Ratio (M-H, Random, 95% CI) | 5.46 [0.30, 98.43] |
| 2 Major bleeding: LMWH vs aspirin | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3 Major bleeding: LMWH vs warfarin | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 4 Major bleeding: vitamin K antagonists vs placebo | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 5 Major bleeding: warfarin vs aspirin | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 6 Major bleeding: antithrombin vs placebo | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |

**Comparison 3. Anticoagulants versus control: symptomatic PE**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Symptomatic PE: LMWH vs placebo | 3 | 1710 | Risk Ratio (M-H, Random, 95% CI) | 0.63 [0.21, 1.91] |
| 1.1 Dalteparin | 2 | 560 | Risk Ratio (M-H, Random, 95% CI) | 1.04 [0.11, 10.25] |
| 1.2 Nadroparin | 1 | 1150 | Risk Ratio (M-H, Random, 95% CI) | 0.50 [0.10, 2.44] |
| 2 Symptomatic PE: LMWH vs aspirin | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3 Symptomatic PE: LMWH vs warfarin | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 4 Symptomatic PE: vitamin K antagonists vs placebo | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 5 Symptomatic PE: warfarin vs aspirin | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

**Comparison 4. Anticoagulants versus control: symptomatic DVT**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Symptomatic DVT: LMWH vs placebo | 4 | 1794 | Risk Ratio (M-H, Random, 95% CI) | 0.60 [0.33, 1.07] |
| 1.1 Dalteparin | 3 | 644 | Risk Ratio (M-H, Random, 95% CI) | 0.67 [0.32, 1.39] |
| 1.2 Nadroparin | 1 | 1150 | Risk Ratio (M-H, Random, 95% CI) | 0.50 [0.19, 1.31] |
| 2 Symptomatic DVT: LMWH vs aspirin | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3 Symptomatic DVT: LMWH vs warfarin | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 4 Symptomatic DVT: vitamin K antagonists vs placebo | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 5 Symptomatic DVT: warfarin vs aspirin | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

**Comparison 5. Anticoagulants versus control: asymptomatic VTE**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Asymptomatic VTE: LMWH vs placebo | 2 | 1682 | Risk Ratio (M-H, Random, 95% CI) | 0.64 [0.27, 1.54] |
| 1.1 Certoparine | 1 | 532 | Risk Ratio (M-H, Random, 95% CI) | 0.56 [0.17, 1.90] |
| 1.2 Nadroparin | 1 | 1150 | Risk Ratio (M-H, Random, 95% CI) | 0.74 [0.21, 2.62] |

### Comparison 6. Anticoagulants versus control: overall VTE

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Overall VTE: LMWH vs placebo | 2 | 1682 | Risk Ratio (M-H, Random, 95% CI) | 0.55 [0.34, 0.88] |
| 1.1 Certoparine | 1 | 532 | Risk Ratio (M-H, Random, 95% CI) | 0.54 [0.27, 1.06] |
| 1.2 Nadroparin | 1 | 1150 | Risk Ratio (M-H, Random, 95% CI) | 0.56 [0.29, 1.08] |

### Comparison 7. Anticoagulants versus control: minor bleeding

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Minor bleeding: LMWH vs placebo | 4 | 1746 | Risk Ratio (M-H, Random, 95% CI) | 1.04 [0.76, 1.42] |
| 1.1 Dalteparine | 3 | 596 | Risk Ratio (M-H, Random, 95% CI) | 1.14 [0.63, 2.04] |
| 1.2 Nadroparin | 1 | 1150 | Risk Ratio (M-H, Random, 95% CI) | 1.00 [0.69, 1.45] |
| 2 Minor bleeding: LMWH vs aspirin | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3 Minor bleeding: LMWH vs warfarin | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 4 Minor bleeding: vitamin K antagonists vs placebo | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 5 Minor bleeding: warfarin vs aspirin | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

### Comparison 8. Anticoagulants versus control: one-year mortality

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 One-year mortality: LMWH vs placebo | 4 | 1848 | Risk Ratio (M-H, Random, 95% CI) | 1.04 [0.92, 1.16] |
| 1.1 Dalteparine | 3 | 698 | Risk Ratio (M-H, Random, 95% CI) | 1.04 [0.86, 1.26] |
| 1.2 Nadroparin | 1 | 1150 | Risk Ratio (M-H, Random, 95% CI) | 1.06 [0.92, 1.23] |

**Comparison 9. Anticoagulants versus control: symptomatic arterial thromboembolism**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Symptomatic arterial thromboembolism: LMWH vs placebo | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 1.1 Nadroparin | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2 Symptomatic arterial thromboembolism: LMWH vs aspirin | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3 Symptomatic arterial thromboembolism: LMWH vs warfarin | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 4 Symptomatic arterial thromboembolism: vitamin K antagonists vs placebo | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 5 Symptomatic arterial thromboembolism: warfarin vs aspirin | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

**Comparison 10. Anticoagulants versus control: superficial thrombophlebitis**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Superficial thrombophlebitis: LMWH vs placebo | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 1.1 Nadroparin | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |

**Comparison 11. Anticoagulants versus control: serious adverse events**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Serious adverse events: LMWH vs placebo | 3 | 1372 | Risk Ratio (M-H, Random, 95% CI) | 1.21 [0.54, 2.69] |
| 1.1 Dalteparine | 2 | 222 | Risk Ratio (M-H, Random, 95% CI) | 2.50 [0.65, 9.64] |
| 1.2 Nadroparin | 1 | 1150 | Risk Ratio (M-H, Random, 95% CI) | 0.89 [0.68, 1.17] |

## Comparison 12. Anticoagulants versus control: symptomatic VTE in lung cancer

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Symptomatic VTE in lung cancer: LMWH vs control | 3 | 895 | Odds Ratio (M-H, Fixed, 95% CI) | 0.54 [0.27, 1.09] |

## Comparison 13. Anticoagulants versus control: major bleeding in lung cancer

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Major bleeding in lung cancer: LMWH vs control | 2 | 825 | Odds Ratio (M-H, Fixed, 95% CI) | 1.73 [0.65, 4.57] |

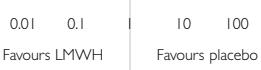
### Analysis 1.1. Comparison 1 Anticoagulants versus control: symptomatic VTE, Outcome 1 Symptomatic VTE: LMWH vs placebo.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 1 Anticoagulants versus control: symptomatic VTE

Outcome: 1 Symptomatic VTE: LMWH vs placebo

| Study or subgroup | LMWH n/N | placebo n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 Dalteparine | | | | | |
| Altinbas 2004 | 0/42 | 1/42 | | 1.6 % | 0.33 [ 0.01, 7.96 ] |
| Kakkar 2004 | 4/190 | 5/184 | | 9.7 % | 0.77 [ 0.21, 2.84 ] |
| Perry 2010 | 11/99 | 13/87 | | 29.2 % | 0.74 [ 0.35, 1.57 ] |
| Sideras 2006 | 4/68 | 5/70 | | 10.1 % | 0.82 [ 0.23, 2.94 ] |
| **Subtotal (95% CI)** | **399** | **383** | | **50.6 %** | **0.75 [ 0.42, 1.32 ]** |
| Total events: 19 (LMWH), 24 (placebo) | | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.27$, df = 3 (P = 0.96); $I^2 = 0.0\%$ | | | | | |
| Test for overall effect: Z = 1.01 (P = 0.31) | | | | | |
| 2 Certoparine | | | | | |
| Haas 2005 | 8/268 | 15/264 | | 23.2 % | 0.53 [ 0.23, 1.22 ] |

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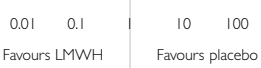
| Study or subgroup | LMWH n/N | placebo n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| **Subtotal (95% CI)** | **268** | **264** | | **23.2 %** | **0.53 [ 0.23, 1.22 ]** |
| Total events: 8 (LMWH), 15 (placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.50 (P = 0.13) | | | | | |
| 3 Nadroparin | | | | | |
| Agnelli 2009 | 12/769 | 12/381 | | 26.2 % | 0.50 [ 0.22, 1.09 ] |
| **Subtotal (95% CI)** | **769** | **381** | | **26.2 %** | **0.50 [ 0.22, 1.09 ]** |
| Total events: 12 (LMWH), 12 (placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.74 (P = 0.082) | | | | | |
| **Total (95% CI)** | **1436** | **1028** | | **100.0 %** | **0.62 [ 0.41, 0.93 ]** |
| Total events: 39 (LMWH), 51 (placebo) | | | | | |
| Heterogeneity: $Tau^2$ = 0.0; $Chi^2$ = 1.14, df = 5 (P = 0.95); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 2.33 (P = 0.020) | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.86, df = 2 (P = 0.65), $I^2$ =0.0% | | | | | |



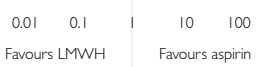

**Analysis 1.2. Comparison 1 Anticoagulants versus control: symptomatic VTE, Outcome 2 Symptomatic VTE: LMWH vs aspirin.**

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 1 Anticoagulants versus control: symptomatic VTE

Outcome: 2 Symptomatic VTE: LMWH vs aspirin

| Study or subgroup | LMWH n/N | aspirin n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| Palumbo 2011 | 6/219 | 12/220 | | 0.50 [ 0.19, 1.31 ] |



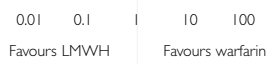
### Analysis 1.3. Comparison 1 Anticoagulants versus control: symptomatic VTE, Outcome 3 Symptomatic VTE: LMWH vs warfarin.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 1 Anticoagulants versus control: symptomatic VTE

Outcome: 3 Symptomatic VTE: LMWH vs warfarin

| Study or subgroup | LMWH n/N | warfarin n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| Palumbo 2011 | 6/219 | 18/220 | | 0.33 [ 0.14, 0.83 ] |



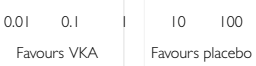

### Analysis 1.4. Comparison 1 Anticoagulants versus control: symptomatic VTE, Outcome 4 Symptomatic VTE: vitamin K antagonists vs placebo.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 1 Anticoagulants versus control: symptomatic VTE

Outcome: 4 Symptomatic VTE: vitamin K antagonists vs placebo

| Study or subgroup | VKA n/N | placebo n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Levine 1994 | 1/152 | 7/159 | | 0.15 [ 0.02, 1.20 ] |

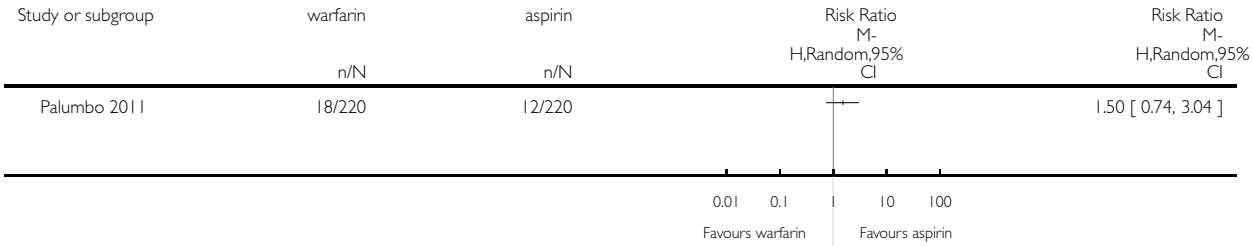


### Analysis 1.5. Comparison 1 Anticoagulants versus control: symptomatic VTE, Outcome 5 Symptomatic VTE: warfarin vs aspirin.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 1 Anticoagulants versus control: symptomatic VTE

Outcome: 5 Symptomatic VTE: warfarin vs aspirin

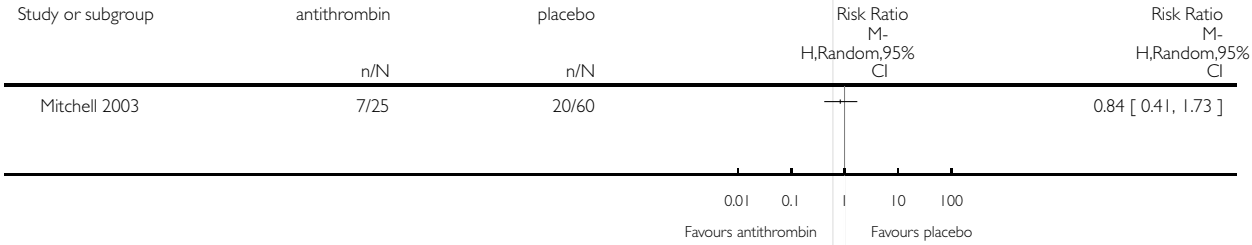



### Analysis 1.6. Comparison 1 Anticoagulants versus control: symptomatic VTE, Outcome 6 Symptomatic VTE: antithrombin vs placebo.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 1 Anticoagulants versus control: symptomatic VTE

Outcome: 6 Symptomatic VTE: antithrombin vs placebo

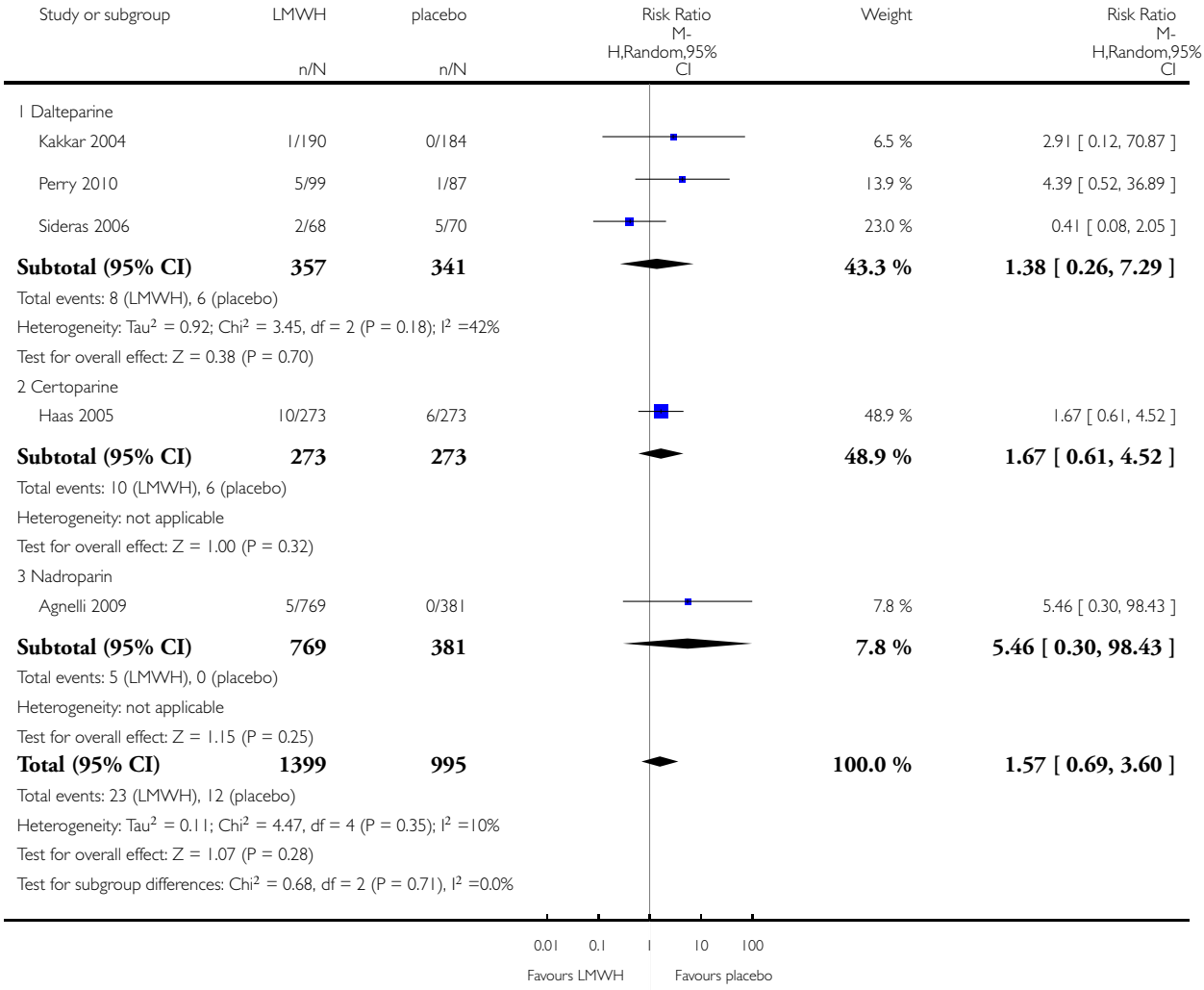


## Analysis 2.1. Comparison 2 Anticoagulants versus control: major bleeding, Outcome 1 Major bleeding: LMWH vs placebo.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 2 Anticoagulants versus control: major bleeding

Outcome: 1 Major bleeding: LMWH vs placebo

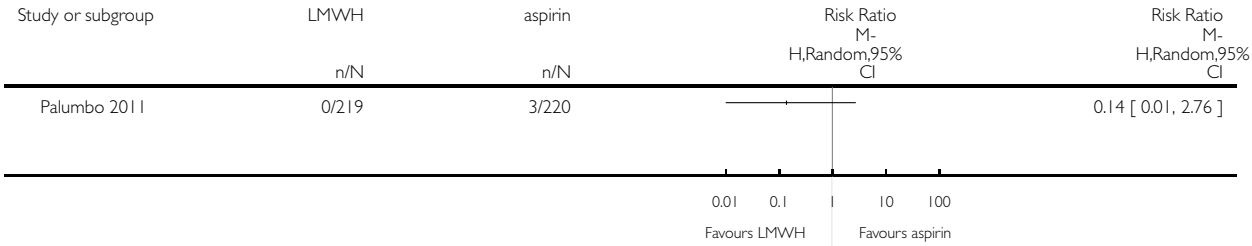


### Analysis 2.2. Comparison 2 Anticoagulants versus control: major bleeding, Outcome 2 Major bleeding: LMWH vs aspirin.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 2 Anticoagulants versus control: major bleeding

Outcome: 2 Major bleeding: LMWH vs aspirin

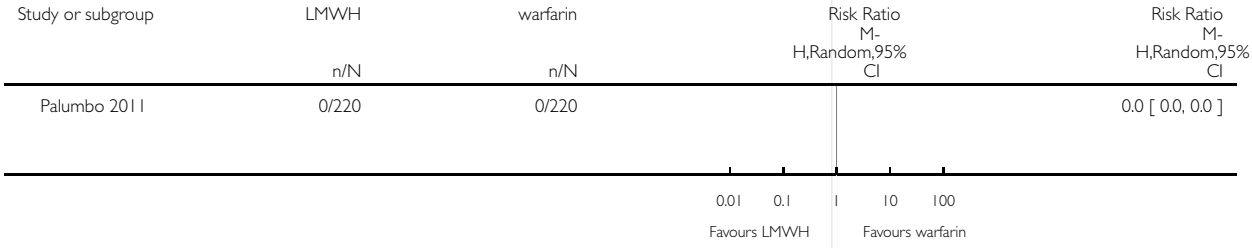



### Analysis 2.3. Comparison 2 Anticoagulants versus control: major bleeding, Outcome 3 Major bleeding: LMWH vs warfarin.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 2 Anticoagulants versus control: major bleeding

Outcome: 3 Major bleeding: LMWH vs warfarin

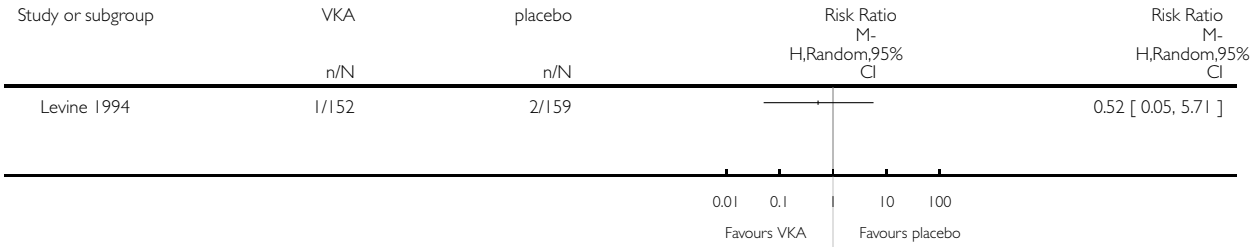


### Analysis 2.4. Comparison 2 Anticoagulants versus control: major bleeding, Outcome 4 Major bleeding: vitamin K antagonists vs placebo.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 2 Anticoagulants versus control: major bleeding

Outcome: 4 Major bleeding: vitamin K antagonists vs placebo

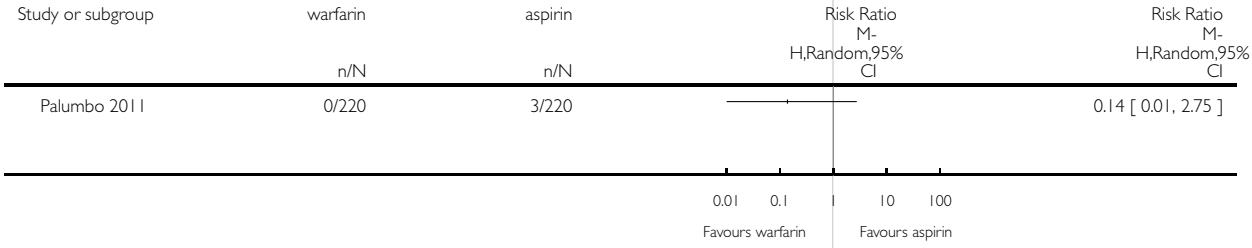



### Analysis 2.5. Comparison 2 Anticoagulants versus control: major bleeding, Outcome 5 Major bleeding: warfarin vs aspirin.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 2 Anticoagulants versus control: major bleeding

Outcome: 5 Major bleeding: warfarin vs aspirin



### Analysis 2.6. Comparison 2 Anticoagulants versus control: major bleeding, Outcome 6 Major bleeding: antithrombin vs placebo.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 2 Anticoagulants versus control: major bleeding

Outcome: 6 Major bleeding: antithrombin vs placebo

| Study or subgroup | antithrombin n/N | placebo n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Mitchell 2003 | 0/25 | 1/60 | | 0.78 [ 0.03, 18.57 ] |

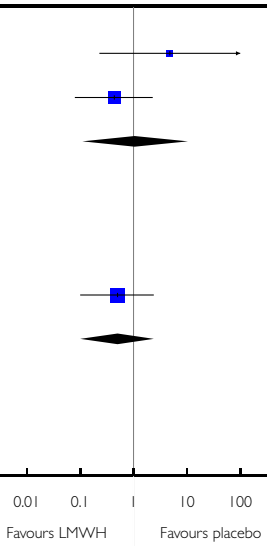

### Analysis 3.1. Comparison 3 Anticoagulants versus control: symptomatic PE, Outcome 1 Symptomatic PE: LMWH vs placebo.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 3 Anticoagulants versus control: symptomatic PE

Outcome: 1 Symptomatic PE: LMWH vs placebo

| Study or subgroup | LMWH n/N | placebo n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 Dalteparin | | | | | |
| Kakkar 2004 | 2/190 | 0/184 | | 13.1 % | 4.84 [ 0.23, 100.20 ] |
| Perry 2010 | 2/99 | 4/87 | | 41.5 % | 0.44 [ 0.08, 2.34 ] |
| **Subtotal (95% CI)** | **289** | **271** | | **54.6 %** | **1.04 [ 0.11, 10.25 ]** |
| Total events: 4 (LMWH), 4 (placebo) | | | | | |
| Heterogeneity: $Tau^2$ = 1.40; $Chi^2$ = 1.90, df = 1 (P = 0.17); $I^2$ =47% | | | | | |
| Test for overall effect: Z = 0.03 (P = 0.97) | | | | | |
| 2 Nadroparin | | | | | |
| Agnelli 2009 | 3/769 | 3/381 | | 45.4 % | 0.50 [ 0.10, 2.44 ] |
| **Subtotal (95% CI)** | **769** | **381** | | **45.4 %** | **0.50 [ 0.10, 2.44 ]** |
| Total events: 3 (LMWH), 3 (placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.86 (P = 0.39) | | | | | |

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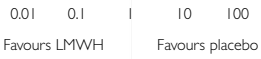
| Study or subgroup | LMWH n/N | placebo n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| **Total (95% CI)** | **1058** | **652** | | **100.0 %** | **0.63 [ 0.21, 1.91 ]** |

Total events: 7 (LMWH), 7 (placebo)

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 2.07$, df = 2 (P = 0.36); $I^2 = 3\%$

Test for overall effect: Z = 0.81 (P = 0.42)

Test for subgroup differences: $Chi^2 = 0.27$, df = 1 (P = 0.60), $I^2 = 0.0\%$



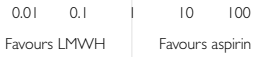

**Analysis 3.2. Comparison 3 Anticoagulants versus control: symptomatic PE, Outcome 2 Symptomatic PE: LMWH vs aspirin.**

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 3 Anticoagulants versus control: symptomatic PE

Outcome: 2 Symptomatic PE: LMWH vs aspirin

| Study or subgroup | LMWH n/N | aspirin n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| Palumbo 2011 | 0/219 | 4/220 | | 0.11 [ 0.01, 2.06 ] |

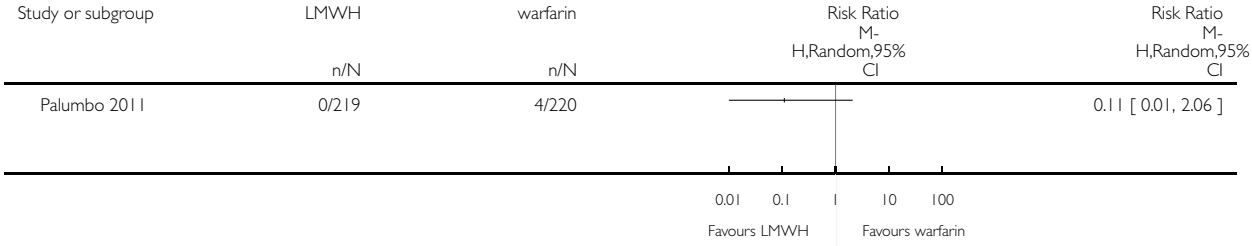


### Analysis 3.3. Comparison 3 Anticoagulants versus control: symptomatic PE, Outcome 3 Symptomatic PE: LMWH vs warfarin.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 3 Anticoagulants versus control: symptomatic PE

Outcome: 3 Symptomatic PE: LMWH vs warfarin

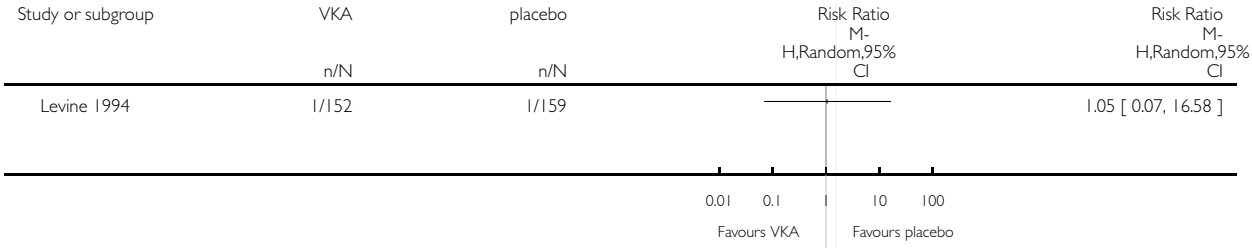



### Analysis 3.4. Comparison 3 Anticoagulants versus control: symptomatic PE, Outcome 4 Symptomatic PE: vitamin K antagonists vs placebo.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 3 Anticoagulants versus control: symptomatic PE

Outcome: 4 Symptomatic PE: vitamin K antagonists vs placebo

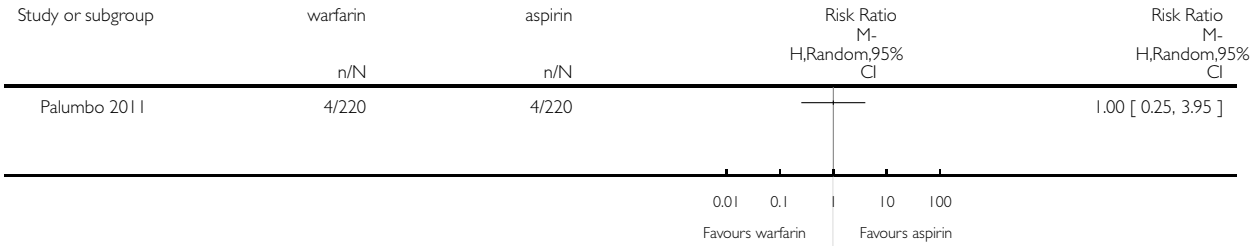


### Analysis 3.5. Comparison 3 Anticoagulants versus control: symptomatic PE, Outcome 5 Symptomatic PE: warfarin vs aspirin.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 3 Anticoagulants versus control: symptomatic PE

Outcome: 5 Symptomatic PE: warfarin vs aspirin

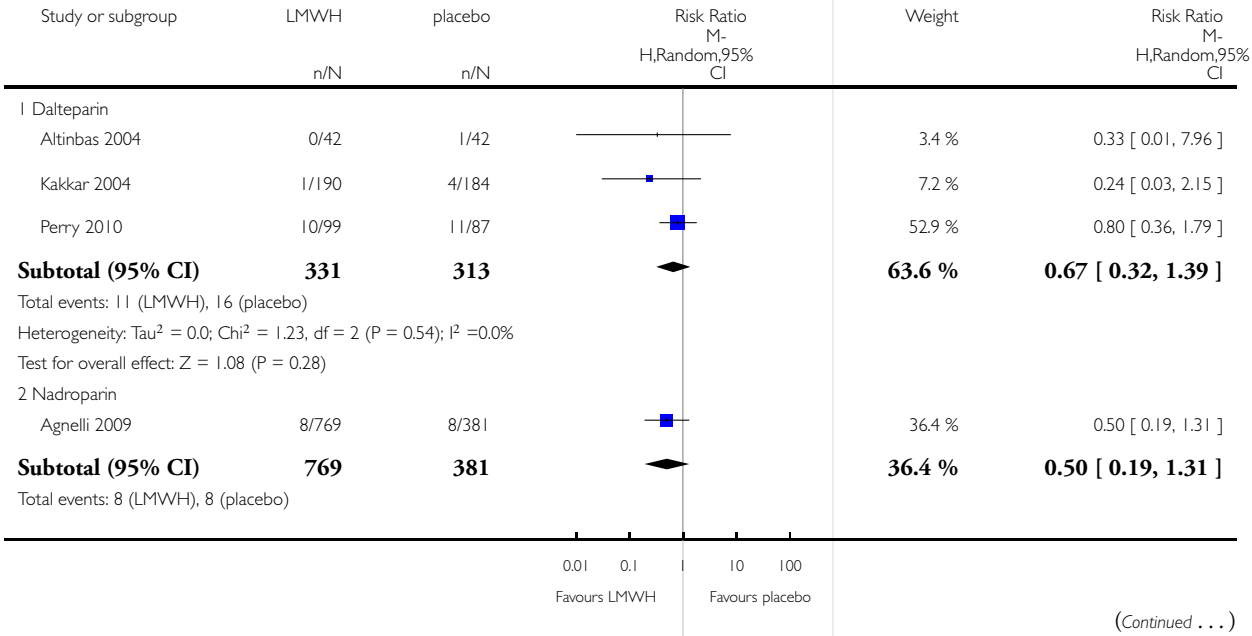



### Analysis 4.1. Comparison 4 Anticoagulants versus control: symptomatic DVT, Outcome 1 Symptomatic DVT: LMWH vs placebo.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 4 Anticoagulants versus control: symptomatic DVT

Outcome: 1 Symptomatic DVT: LMWH vs placebo

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| Study or subgroup | LMWH n/N | placebo n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.42 (P = 0.16) | | | | | |
| **Total (95% CI)** | **1100** | **694** | | **100.0 %** | **0.60 [ 0.33, 1.07 ]** |
| Total events: 19 (LMWH), 24 (placebo) | | | | | |
| Heterogeneity: $Tau^2$ = 0.0; $Chi^2$ = 1.44, df = 3 (P = 0.70); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 1.72 (P = 0.086) | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.22, df = 1 (P = 0.64), $I^2$ =0.0% | | | | | |

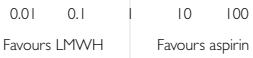

**Analysis 4.2. Comparison 4 Anticoagulants versus control: symptomatic DVT, Outcome 2 Symptomatic DVT: LMWH vs aspirin.**

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 4 Anticoagulants versus control: symptomatic DVT

Outcome: 2 Symptomatic DVT: LMWH vs aspirin

| Study or subgroup | LMWH n/N | aspirin n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| Palumbo 2011 | 6/220 | 8/220 | | 0.75 [ 0.26, 2.13 ] |

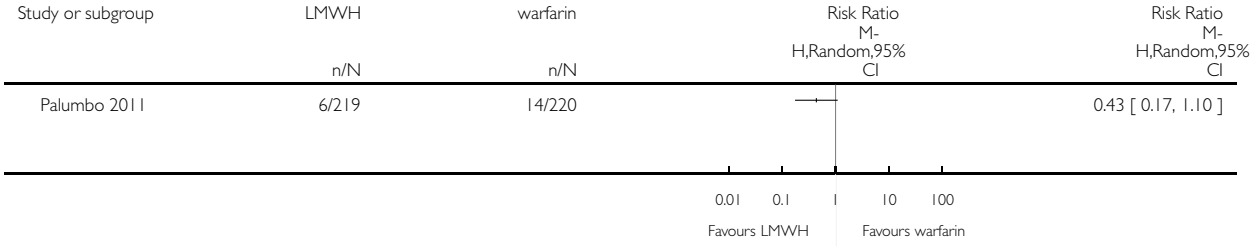


### Analysis 4.3. Comparison 4 Anticoagulants versus control: symptomatic DVT, Outcome 3 Symptomatic DVT: LMWH vs warfarin.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 4 Anticoagulants versus control: symptomatic DVT

Outcome: 3 Symptomatic DVT: LMWH vs warfarin

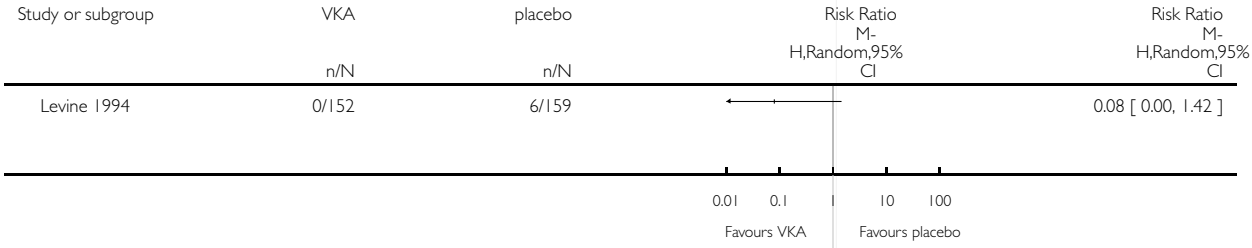



### Analysis 4.4. Comparison 4 Anticoagulants versus control: symptomatic DVT, Outcome 4 Symptomatic DVT: vitamin K antagonists vs placebo.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 4 Anticoagulants versus control: symptomatic DVT

Outcome: 4 Symptomatic DVT: vitamin K antagonists vs placebo

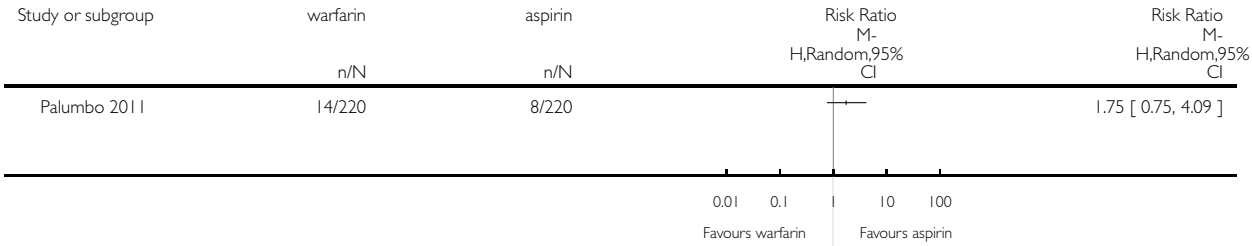


### Analysis 4.5. Comparison 4 Anticoagulants versus control: symptomatic DVT, Outcome 5 Symptomatic DVT: warfarin vs aspirin.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 4 Anticoagulants versus control: symptomatic DVT

Outcome: 5 Symptomatic DVT: warfarin vs aspirin

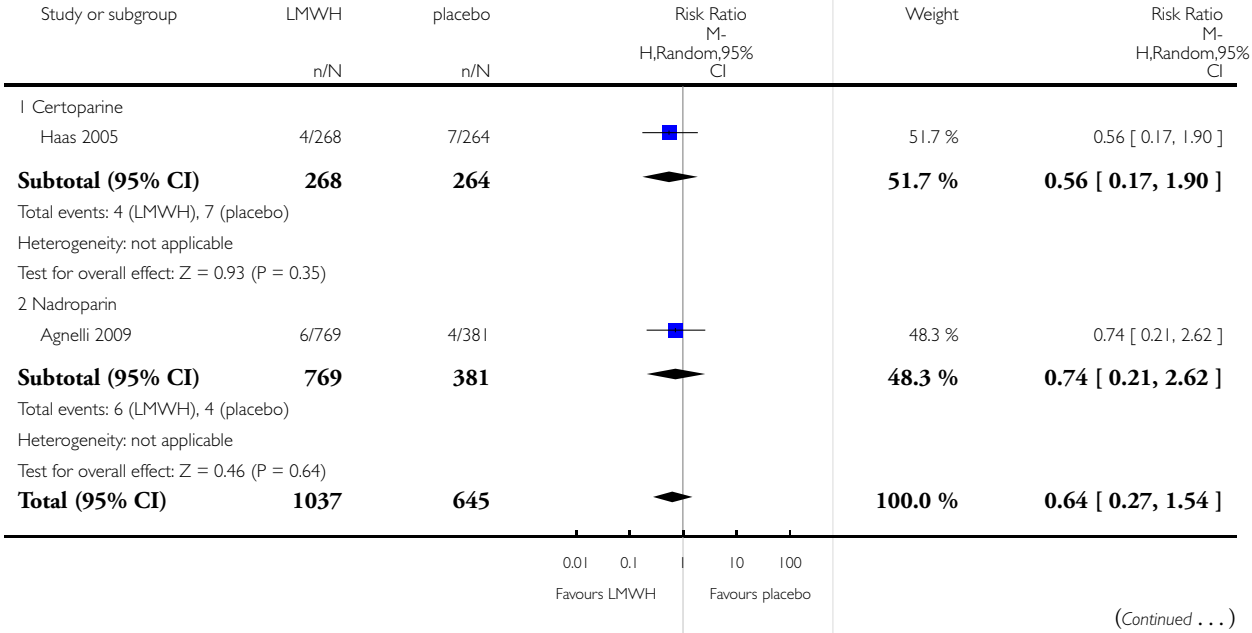



### Analysis 5.1. Comparison 5 Anticoagulants versus control: asymptomatic VTE, Outcome 1 Asymptomatic VTE: LMWH vs placebo.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 5 Anticoagulants versus control: asymptomatic VTE

Outcome: 1 Asymptomatic VTE: LMWH vs placebo




(*Continued* . . . )

(. . . *Continued*)

| Study or subgroup | LMWH n/N | placebo n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Total events: 10 (LMWH), 11 (placebo) | | | | | |
| Heterogeneity: Tau² = 0.0; Chi² = 0.10, df = 1 (P = 0.76); I² =0.0% | | | | | |
| Test for overall effect: Z = 0.99 (P = 0.32) | | | | | |
| Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.76), I² =0.0% | | | | | |

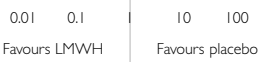

**Analysis 6.1. Comparison 6 Anticoagulants versus control: overall VTE, Outcome 1 Overall VTE: LMWH vs placebo.**

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 6 Anticoagulants versus control: overall VTE

Outcome: 1 Overall VTE: LMWH vs placebo

| Study or subgroup | LMWH n/N | placebo n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 Certoparine | | | | | |
| Haas 2005 | 12/268 | 22/264 | | 48.5 % | 0.54 [ 0.27, 1.06 ] |
| **Subtotal (95% CI)** | **268** | **264** | | **48.5 %** | **0.54 [ 0.27, 1.06 ]** |
| Total events: 12 (LMWH), 22 (placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.78 (P = 0.074) | | | | | |
| 2 Nadroparin | | | | | |
| Agnelli 2009 | 18/769 | 16/381 | | 51.5 % | 0.56 [ 0.29, 1.08 ] |
| **Subtotal (95% CI)** | **769** | **381** | | **51.5 %** | **0.56 [ 0.29, 1.08 ]** |
| Total events: 18 (LMWH), 16 (placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.73 (P = 0.084) | | | | | |
| **Total (95% CI)** | **1037** | **645** | | **100.0 %** | **0.55 [ 0.34, 0.88 ]** |
| Total events: 30 (LMWH), 38 (placebo) | | | | | |
| Heterogeneity: Tau² = 0.0; Chi² = 0.01, df = 1 (P = 0.94); I² =0.0% | | | | | |
| Test for overall effect: Z = 2.48 (P = 0.013) | | | | | |
| Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² =0.0% | | | | | |

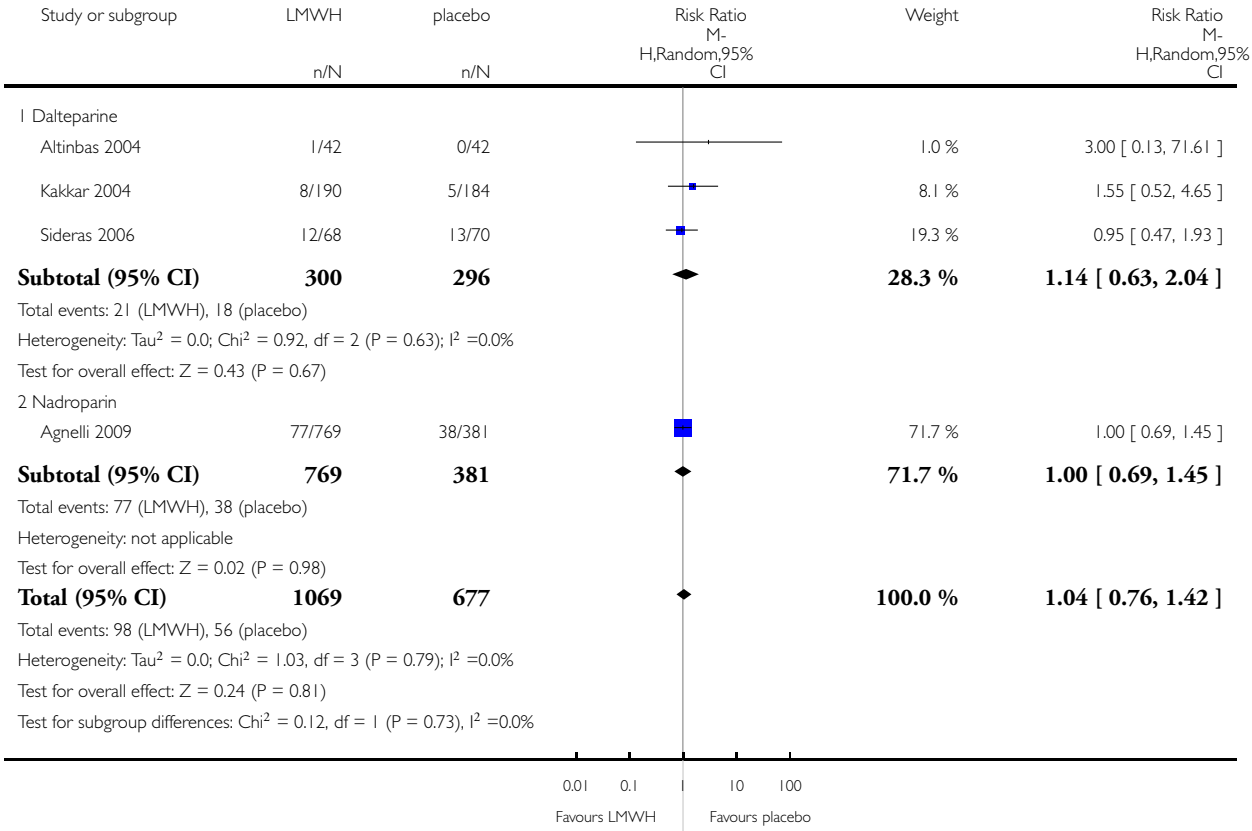


## Analysis 7.1. Comparison 7 Anticoagulants versus control: minor bleeding, Outcome 1 Minor bleeding: LMWH vs placebo.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 7 Anticoagulants versus control: minor bleeding

Outcome: 1 Minor bleeding: LMWH vs placebo

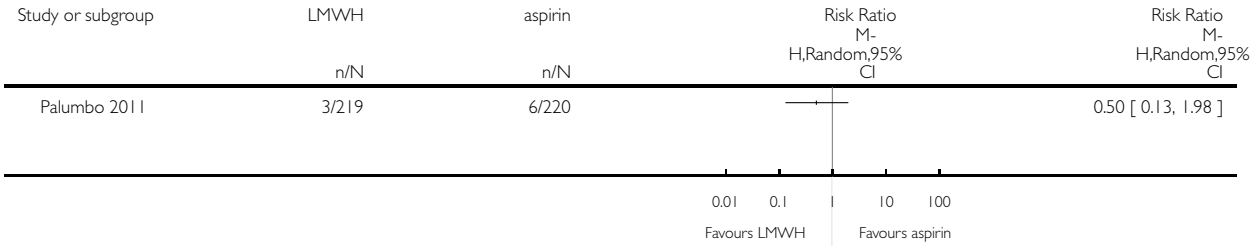


### Analysis 7.2. Comparison 7 Anticoagulants versus control: minor bleeding, Outcome 2 Minor bleeding: LMWH vs aspirin.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 7 Anticoagulants versus control: minor bleeding

Outcome: 2 Minor bleeding: LMWH vs aspirin

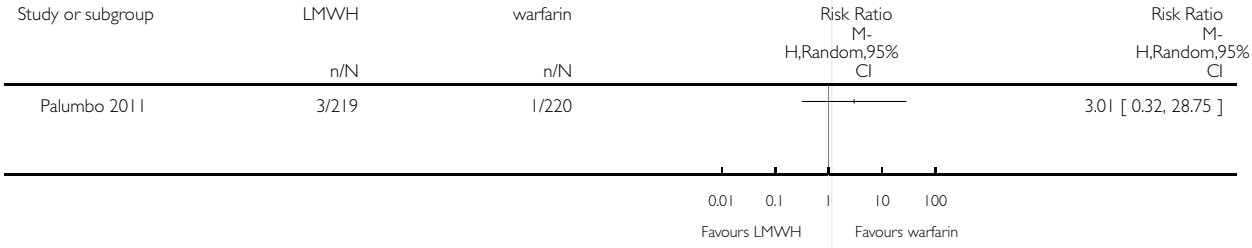



### Analysis 7.3. Comparison 7 Anticoagulants versus control: minor bleeding, Outcome 3 Minor bleeding: LMWH vs warfarin.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 7 Anticoagulants versus control: minor bleeding

Outcome: 3 Minor bleeding: LMWH vs warfarin

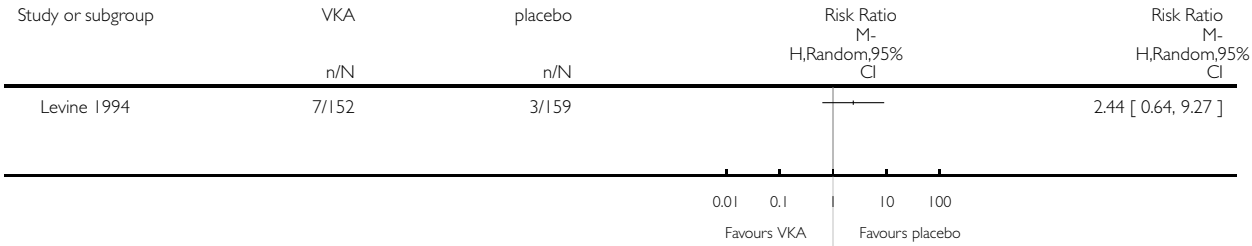


### Analysis 7.4. Comparison 7 Anticoagulants versus control: minor bleeding, Outcome 4 Minor bleeding: vitamin K antagonists vs placebo.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 7 Anticoagulants versus control: minor bleeding

Outcome: 4 Minor bleeding: vitamin K antagonists vs placebo

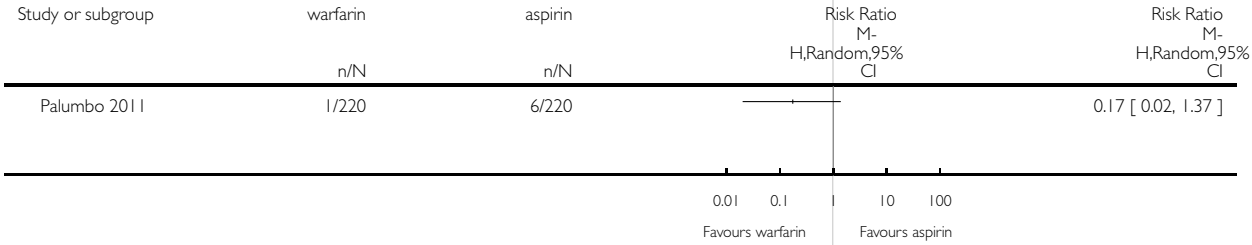



### Analysis 7.5. Comparison 7 Anticoagulants versus control: minor bleeding, Outcome 5 Minor bleeding: warfarin vs aspirin.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 7 Anticoagulants versus control: minor bleeding

Outcome: 5 Minor bleeding: warfarin vs aspirin



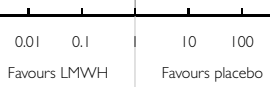
## Analysis 8.1. Comparison 8 Anticoagulants versus control: one-year mortality, Outcome 1 One-year mortality: LMWH vs placebo.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 8 Anticoagulants versus control: one-year mortality

Outcome: 1 One-year mortality: LMWH vs placebo

| Study or subgroup | LMWH n/N | placebo n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 Dalteparine | | | | | |
| Kakkar 2004 | 105/190 | 112/184 | | 32.3 % | 0.91 [ 0.76, 1.08 ] |
| Perry 2010 | 45/99 | 32/87 | | 10.0 % | 1.24 [ 0.87, 1.75 ] |
| Sideras 2006 | 45/68 | 41/70 | | 16.9 % | 1.13 [ 0.87, 1.47 ] |
| **Subtotal (95% CI)** | **357** | **341** | | **59.3 %** | **1.04 [ 0.86, 1.26 ]** |
| Total events: 195 (LMWH), 185 (placebo) | | | | | |
| Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 3.47$, df = 2 (P = 0.18); $I^2 = 42\%$ | | | | | |
| Test for overall effect: Z = 0.39 (P = 0.69) | | | | | |
| 2 Nadroparin | | | | | |
| Agnelli 2009 | 333/769 | 155/381 | | 40.7 % | 1.06 [ 0.92, 1.23 ] |
| **Subtotal (95% CI)** | **769** | **381** | | **40.7 %** | **1.06 [ 0.92, 1.23 ]** |
| Total events: 333 (LMWH), 155 (placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.84 (P = 0.40) | | | | | |
| **Total (95% CI)** | **1126** | **722** | | **100.0 %** | **1.04 [ 0.92, 1.16 ]** |
| Total events: 528 (LMWH), 340 (placebo) | | | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.81$, df = 3 (P = 0.28); $I^2 = 21\%$ | | | | | |
| Test for overall effect: Z = 0.61 (P = 0.54) | | | | | |
| Test for subgroup differences: $Chi^2 = 0.04$, df = 1 (P = 0.84), $I^2 = 0.0\%$ | | | | | |

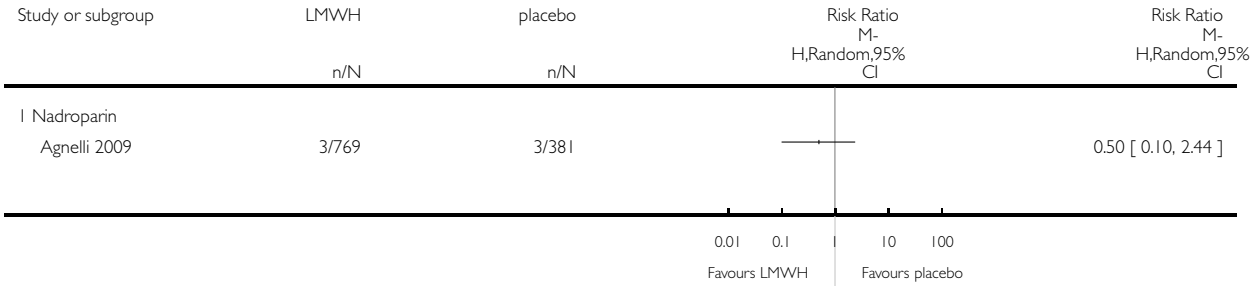


## Analysis 9.1. Comparison 9 Anticoagulants versus control: symptomatic arterial thromboembolism, Outcome 1 Symptomatic arterial thromboembolism: LMWH vs placebo.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 9 Anticoagulants versus control: symptomatic arterial thromboembolism

Outcome: 1 Symptomatic arterial thromboembolism: LMWH vs placebo

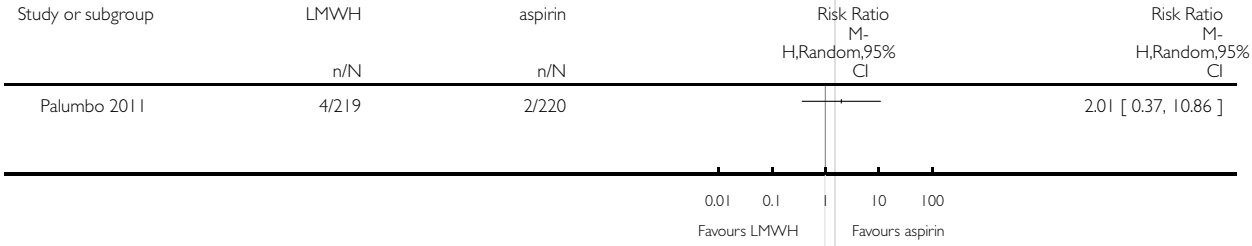



## Analysis 9.2. Comparison 9 Anticoagulants versus control: symptomatic arterial thromboembolism, Outcome 2 Symptomatic arterial thromboembolism: LMWH vs aspirin.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 9 Anticoagulants versus control: symptomatic arterial thromboembolism

Outcome: 2 Symptomatic arterial thromboembolism: LMWH vs aspirin

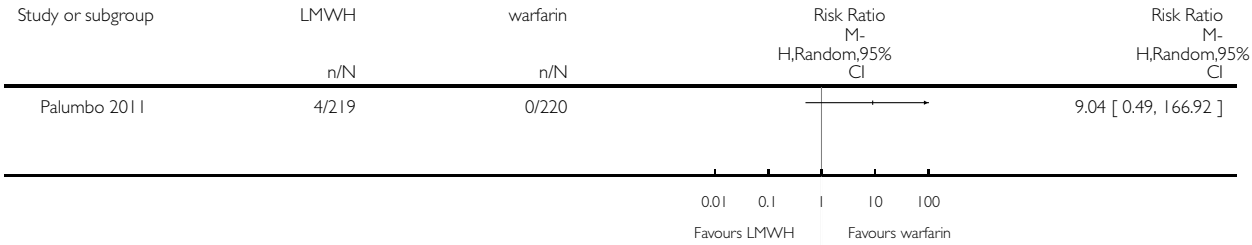


### Analysis 9.3. Comparison 9 Anticoagulants versus control: symptomatic arterial thromboembolism, Outcome 3 Symptomatic arterial thromboembolism: LMWH vs warfarin.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 9 Anticoagulants versus control: symptomatic arterial thromboembolism

Outcome: 3 Symptomatic arterial thromboembolism: LMWH vs warfarin

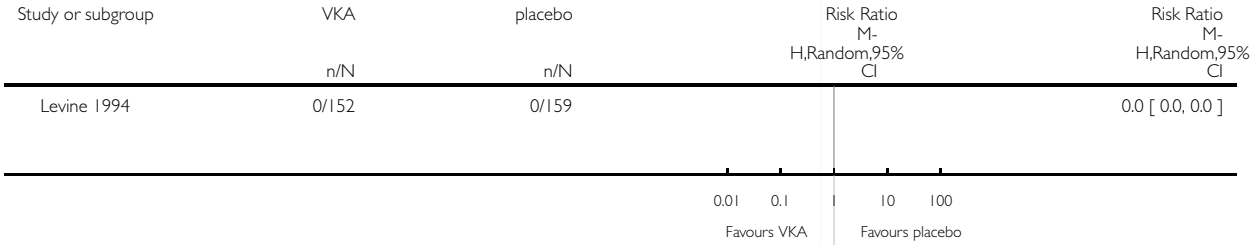



### Analysis 9.4. Comparison 9 Anticoagulants versus control: symptomatic arterial thromboembolism, Outcome 4 Symptomatic arterial thromboembolism: vitamin K antagonists vs placebo.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 9 Anticoagulants versus control: symptomatic arterial thromboembolism

Outcome: 4 Symptomatic arterial thromboembolism: vitamin K antagonists vs placebo

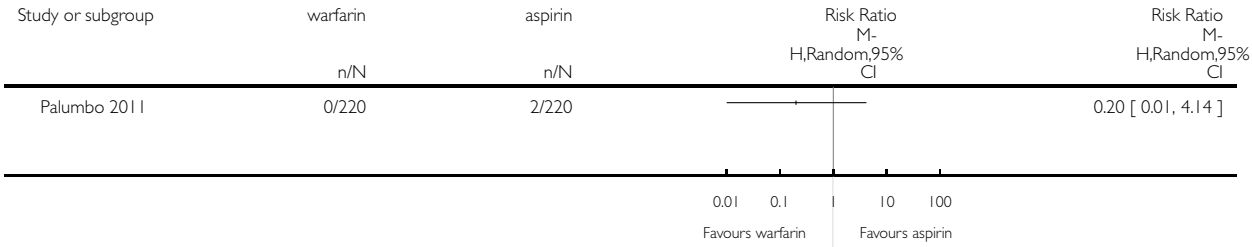


### Analysis 9.5. Comparison 9 Anticoagulants versus control: symptomatic arterial thromboembolism, Outcome 5 Symptomatic arterial thromboembolism: warfarin vs aspirin.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 9 Anticoagulants versus control: symptomatic arterial thromboembolism

Outcome: 5 Symptomatic arterial thromboembolism: warfarin vs aspirin

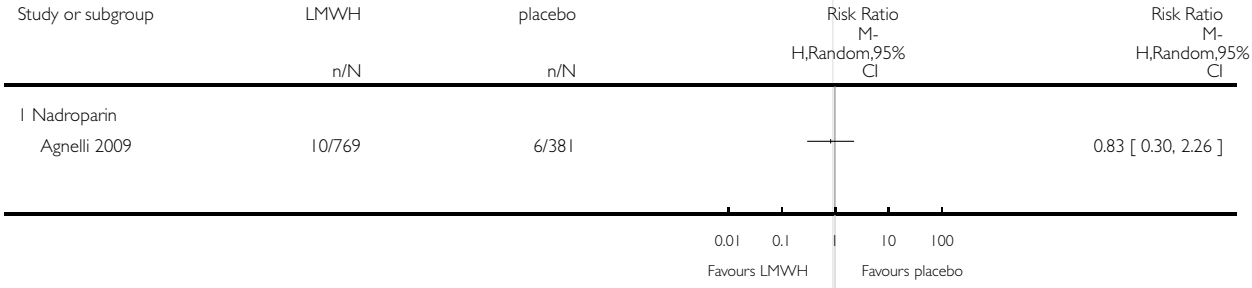



### Analysis 10.1. Comparison 10 Anticoagulants versus control: superficial thrombophlebitis, Outcome 1 Superficial thrombophlebitis: LMWH vs placebo.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 10 Anticoagulants versus control: superficial thrombophlebitis

Outcome: 1 Superficial thrombophlebitis: LMWH vs placebo



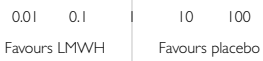
## Analysis 11.1. Comparison 11 Anticoagulants versus control: serious adverse events, Outcome 1 Serious adverse events: LMWH vs placebo.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 11 Anticoagulants versus control: serious adverse events

Outcome: 1 Serious adverse events: LMWH vs placebo

| Study or subgroup | LMWH n/N | placebo n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 Dalteparine | | | | | |
| Altinbas 2004 | 5/42 | 1/42 | | 12.2 % | 5.00 [ 0.61, 40.99 ] |
| Sideras 2006 | 3/68 | 2/70 | | 16.4 % | 1.54 [ 0.27, 8.96 ] |
| **Subtotal (95% CI)** | **110** | **112** | | **28.6 %** | **2.50 [ 0.65, 9.64 ]** |
| Total events: 8 (LMWH), 3 (placebo) | | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.72$, df = 1 (P = 0.40); $I^2 = 0.0\%$ | | | | | |
| Test for overall effect: Z = 1.33 (P = 0.18) | | | | | |
| 2 Nadroparin | | | | | |
| Agnelli 2009 | 121/769 | 67/381 | | 71.4 % | 0.89 [ 0.68, 1.17 ] |
| **Subtotal (95% CI)** | **769** | **381** | | **71.4 %** | **0.89 [ 0.68, 1.17 ]** |
| Total events: 121 (LMWH), 67 (placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.80 (P = 0.42) | | | | | |
| **Total (95% CI)** | **879** | **493** | | **100.0 %** | **1.21 [ 0.54, 2.69 ]** |
| Total events: 129 (LMWH), 70 (placebo) | | | | | |
| Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 2.88$, df = 2 (P = 0.24); $I^2 = 31\%$ | | | | | |
| Test for overall effect: Z = 0.46 (P = 0.64) | | | | | |
| Test for subgroup differences: $Chi^2 = 2.15$, df = 1 (P = 0.14), $I^2 = 53\%$ | | | | | |



## Analysis 12.1. Comparison 12 Anticoagulants versus control: symptomatic VTE in lung cancer, Outcome 1 Symptomatic VTE in lung cancer: LMWH vs control.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 12 Anticoagulants versus control: symptomatic VTE in lung cancer

Outcome: 1 Symptomatic VTE in lung cancer: LMWH vs control

| Study or subgroup | LMWH n/N | control n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Agnelli 2009 | 7/199 | 4/80 | | 25.4 % | 0.69 [ 0.20, 2.43 ] |
| Altinbas 2004 | 0/42 | 1/42 | | 6.8 % | 0.33 [ 0.01, 8.22 ] |
| Haas 2005 | 8/268 | 15/264 | | 67.7 % | 0.51 [ 0.21, 1.23 ] |
| **Total (95% CI)** | **509** | **386** | | **100.0 %** | **0.54 [ 0.27, 1.09 ]** |

Total events: 15 (LMWH), 20 (control)

Heterogeneity: $Chi^2 = 0.26$, df = 2 (P = 0.88); $I^2 = 0.0\%$

Test for overall effect: Z = 1.72 (P = 0.086)

Test for subgroup differences: Not applicable


## Analysis 13.1. Comparison 13 Anticoagulants versus control: major bleeding in lung cancer, Outcome 1 Major bleeding in lung cancer: LMWH vs control.

Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 13 Anticoagulants versus control: major bleeding in lung cancer

Outcome: 1 Major bleeding in lung cancer: LMWH vs control

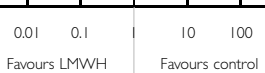
| Study or subgroup | LMWH n/N | control n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Agnelli 2009 | 2/199 | 0/80 | | 10.8 % | 2.04 [ 0.10, 42.92 ] |
| Haas 2005 | 10/273 | 6/273 | | 89.2 % | 1.69 [ 0.61, 4.72 ] |
| **Total (95% CI)** | **472** | **353** | | **100.0 %** | **1.73 [ 0.65, 4.57 ]** |

Total events: 12 (LMWH), 6 (control)

Heterogeneity: $Chi^2 = 0.01$, df = 1 (P = 0.91); $I^2 = 0.0\%$

Test for overall effect: Z = 1.11 (P = 0.27)

Test for subgroup differences: Not applicable



## ADDITIONAL TABLES

**Table 1. Results of stratified analyses on major bleeding**

| Variable | N of trials | N of patients (LMWH) | N of patients (control) | RR (95% CI) | Heterogeneity $I^2$ (%) | P for interaction |
|---|---|---|---|---|---|---|
| | | | | | | |
| **All trials** | 5 | 1399 | 995 | 1.57 (69 to 3.60) | 10% | |
| **Allocation concealment** | | | | | | 0.24 |
| Adequate | 3 | 1058 | 652 | 4.25 (0.94 to 19. 24) | 0% | |
| Inadequate or unclear | 2 | 341 | 343 | 0.96 (0.25 to 3. 66) | 52% | |
| **Blinding of patients** | | | | | | 0.17 |
| Double-blind | 4 | 1331 | 925 | 2.21 (0.96 to 5. 09) | 0% | |
| Inadequate or unclear blinding | 1 | 68 | 70 | 0.41 (0.08 to 2. 05) | N/A | |
| **Intention-to-treat analysis** | | | | | | 0.41 |
| Yes | 1 | 99 | 87 | 4.39 (0.52 to 36. 89) | | |
| No or unclear | 4 | 1300 | 925 | 1.33 (0.54 to 3. 28) | 11.5 | |
| **Definition of bleeding** | | | | | | 0.24 |
| Standard | 3 | 1058 | 652 | 4.25 (0.94 to 19. 24) | 0% | |
| Alternative or unclear | 2 | 341 | 343 | 0.96 (0.25 to 3. 66) | 52.4% | |
| **Age** | | | | | | 0.17 |
| mean > 65 years | 4 | 1331 | 925 | 2.21 (0.96 to 5. 09) | 0% | |

**Table 1. Results of stratified analyses on major bleeding** (*Continued*)

| | | | | | | |
|---|---|---|---|---|---|---|
| mean < 65 years | 1 | 68 | 70 | 0.41 (0.08 to 2. 05) | N/A | |

# APPENDICES

## Appendix 1. CENTRAL search strategy

| | | |
|---|---|---|
| #1 | MeSH descriptor Thrombosis, this term only | 1077 |
| #2 | MeSH descriptor Thromboembolism, this term only | 974 |
| #3 | MeSH descriptor Venous Thromboembolism, this term only | 159 |
| #4 | MeSH descriptor Venous Thrombosis, this term only | 924 |
| #5 | (thromboprophyla* or thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*):ti,ab,kw | 10726 |
| #6 | MeSH descriptor Pulmonary Embolism explode all trees | 818 |
| #7 | (PE or DVT or VTE):ti,ab,kw | 1961 |
| #8 | ((deep near (vein* or ven*) near thromb*) or "blood flow stasis" or "vein stasis" or "venous stasis" or "blood clot"):ti,ab,kw | 2767 |
| #9 | (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8) | 11955 |
| #10 | MeSH descriptor Neoplasms explode all trees | 42654 |
| #11 | (malignan* or neoplas* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or glio* or leukemia or chemotherapy or myeloma or oncology):ti,ab,kw | 79055 |
| #12 | (#10 OR #11) | 80801 |
| #13 | (#9 AND #12) | 1328 |

## Appendix 2. Abbreviations and scientific terms

| Abbreviation | Scientific description | Lay description |
|---|---|---|
| | Anticoagulation therapy | Blood thinning therapy |
| GES | Graduated elastic stockings | Graduated elastic stockings are special socks that improve blood flow in the leg veins and prevent blood from pooling in the legs |
| | Incidence | Number of newly diagnosed diseases, in this review cases of VTE |
| IPC | Intermittent pneumatic compression | A mechanical intervention using an air pump and inflatable leggings to provide pulsing pressure that pushes blood through the veins |
| | Primary prophylaxis | Primary protective treatment aiming at the prevention of disease development |
| | Tromboprophylaxis | Treatment to prevent the development of blood clots |
| VTE | Venous thromboembolism | Blood clots |

## HISTORY

Protocol first published: Issue 5, 2010

Review first published: Issue 2, 2012

## CONTRIBUTIONS OF AUTHORS

Study conception: Di Nisio

Protocol development: Di Nisio, Rutjes, Ferrante, Porreca

Acquisition of data: Di Nisio, Rutjes, Ferrante

Analysis and interpretation of data: Di Nisio, Rutjes, Ferrante, Otten, Porreca

Drafting of the manuscript: Di Nisio, Rutjes

Critical revision of the manuscript for important intellectual content: Di Nisio, Rutjes, Ferrante, Otten, Porreca

Statistical analysis: Di Nisio, Rutjes

Obtained funding: not applicable, no funding available

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None known

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## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol we aimed to combine continuous data from quality of life instruments applying, where appropriate, standard inverse-variance random-effects model meta-analysis (DerSimonian 1986). As none of the included studies reported quality of life data, this was omitted.

In the protocol we planned to explore between trial heterogeneity by stratifying the main outcomes for the following clinical trial characteristics, where relevant: age (below 65 years versus above 65 years); type of cancer, stage of cancer (metastatic versus non metastatic); type of major bleeding (according to definition versus unclear or different definition); concealment of allocation (adequate versus inadequate or unclear); blinding (adequate versus inadequate or unclear); analysis in accordance with the intention-to-treat principle (yes versus no or unclear); trial size; and differences in the use of co-interventions in the trial groups. We planned to use univariate random-effects meta-regression models (Thompson 1999) to determine whether treatment effects were affected by these factors and by three continuous variables at trial level: dosage of intervention, treatment duration and length of follow up. Due to the absence of heterogeneity for the primary efficacy outcome, symptomatic VTE, no such stratified analysis was performed.

Regarding major bleeding, there was not enough contrast to explore the effect of the following trial characteristics: type of cancer, stage of cancer (metastatic versus non metastatic) and differences in the use of co-interventions in the trials groups. Moreover, the number of studies was too limited to allow an analysis for dosage of intervention, treatment duration and length of follow up.